The Journal of Allergy

VOL. 14 MAY, 1943 NO. 4

Original Articles

STUDIES ON THE BLOCKING ANTIBODY IN SERUM OF RAGWEED-TREATED PATIENTS

I. A SEARCH FOR INHIBITING SUBSTANCES IN OTHER TYPES OF IMMUNE SERUM

D. EDWARD FRANK, M.D., AND H. HAROLD GELFAND, M.D.
NEW YORK, N. Y.

COOKE, Barnard, Hebald and Stull[1] demonstrated by means of passive transfer studies on a quantitative basis that more antigen is required to neutralize a ragweed-sensitive patient's serum after treatment with ragweed pollen extract than before treatment. It was thought by Schmidt and Lippard[2] that an increase of reagins in the blood induced by treatment was responsible for this phenomenon, but it seemed more likely to Cooke and others that a new antibody was developed in the serum of treated patients. Because this new antibody was believed to interfere with the interaction of reagin and antigen, it has been termed a "blocking" antibody. That such an antibody is developed in allergic patients as a result of ragweed therapy was further evidenced by the fact that Cooke, Loveless, and Stull[3] succeeded in inducing a similar antibody in nonsensitive subjects by injections of ragweed pollen extract. Cohen and Nelson[4] produced it in the same way in sheep.

By heating treated serum to 56° C. for two hours or more, Loveless[5] was able to inactivate the reagins but not the blocking antibody, and thus proved that the new antibody is thermostable. She felt that the thermostable antibody competed with the reagin in an effort to combine with the antigen in the neutralization test and that the thermostable antibody was the more successful in the contest. However, the reaginic serum can passively sensitize the skin of a nonsensitive subject, while the thermostable antibody alone is unable to do so.

In discussing the work of Scully and Rackemann,[6] Cooke stated that the thermostable antibody shows a high degree of specificity for the antigen inducing it as compared to the skin-sensitizing antibody of the

From the Department of Allergy of Gouverneur Hospital, Department of Hospitals, City of New York.

Read at the Annual Meeting of the American Association for the Study of Allergy, Atlantic City, June 8-9, 1942.

same serum, which usually reacts with a large number of biologically related, and often unrelated, antigens.

On the theory that pooled convalescent sera would include some serum from allergic persons (according to the incidence of allergy in the general population), Tumpeer and Rubens[7] made a search for reagins in convalescent scarlet fever serum but could find no evidence of their presence in sufficient concentration to be demonstrable in the passive transfer test. Moreover, when they diluted high reaginic serum with pooled convalescent scarlet fever sera, they found that successful passive transfer was no longer possible. From this they deduced that an inhibiting substance existed in the convalescent scarlet fever sera. The inhibiting property proved to be strongest in old preserved pooled sera that had been passed through a Berkefeld filter and weakest in fresh sera, nonfiltered sera, and single specimens of serum.

These observations suggested that convalescent sera might contain blocking antibodies similar to those demonstrated by Cooke and by others.[8, 9] The experimental background for this theory is to be found in the work of Hilber,[10] who passively sensitized forty tuberculin-positive children with the serum of an egg-sensitive eczematous patient. After a twenty-four-hour interval, the sensitized sites were tested intracutaneously with tuberculin. The tuberculin reaction was found to be completely inhibited in eleven and partially inhibited in sixteen of the test subjects. The inhibiting phenomenon could not be demonstrated in sites passively prepared with serum from normal children. On the other hand, when sensitized sites were first tested with an injection of egg white antigen and the same sites retested twenty-four hours later with tuberculin, the egg-sensitive serum failed to inhibit the tuberculin reaction. Hilber believed the inhibition to be due to a blocking of the second allergic reaction by egg antibodies previously fixed to the tissue cells and attributed the variations in response to constitutional variations in antibody-fixing capacity of the skin cells.

The present experiments were designed for two specific purposes: (1) to determine whether the serum of patients convalescing from pneumonia, measles, and scarlet fever contained substances capable of blocking the interaction between antigen and reagin from ragweed-sensitive subjects, and (2) to determine whether the serum of patients convalescing from measles and scarlet fever injected into the skin of ragweed-sensitive patients could inhibit the wheal formation from subsequent injection of ragweed antigen into the same sites.

MATERIAL

Wassermann-negative blood from five ragweed-sensitive patients who had not been treated during the preceding season (1941) was collected. The sera were pooled and used as the source of reagin in the ensuing experiments. Serum from another patient, who had been intensively treated with ragweed pollen injections during the 1941 season, was pre-

heated to 56° C. for two hours to inactivate the reagin and used as the source of thermostable antibody. Ragweed pollen antigen, 10,000 protein nitrogen units per cubic centimeter, was appropriately diluted. Blood from one normal, nonatopic subject supplied the serum for the human serum control in every instance in experiments 1 and 2. Serum from a nonallergic patient recovering from lobar pneumonia was the source of convalescent pneumonia serum for experiment 1. Convalescent measles and scarlet fever sera were obtained from the New York Department of Health Laboratories. These sera were prepared in the following manner: Blood from scarlet fever (or measles) patients convalescing in the first, second, third, and fourth months was collected, from which about thirty sera were pooled, dried, and frozen in vacuo. Later they were reconstituted, passed through a Seitz pad and then through a Berkefeld filter, after which merthiolate 1:10,000 was added as a preservative.

PROCEDURE

Experiment 1.—Pooled reaginic sera (R) was mixed with equal quantities of normal human serum (NH) in a series of sterile vials. To each was added another equal volume of ragweed pollen antigen (A) in the following dilutions: 50 units per cubic centimeter, 400 units per cubic centimeter, 700 units per cubic centimeter, 1,000 units per cubic centimeter, 2,000 units per cubic centimeter, and 2,500 units per cubic centimeter. In another series of vials, equal quantities of R and A (in the six dilutions) were mixed with an equal quantity of convalescent pneumonia serum (P). A third series contained a mixture of R plus A plus M (meales convalescent serum). A fourth series was a mixture of R plus A plus SF (scarlet fever convalescent serum). A fifth contained R plus A plus S (physiologic saline), and a sixth, R plus A plus Th (thermostable antibody serum). The dilutions of the antigen in series 5 were extended beyond 2,500 units per cubic centimeter to 7,000 units per cubic centimeter, in anticipation of a higher neutralization titer in the thermostable antibody serum. All the mixtures remained in the icebox for at least twenty-four hours.

The Th, or thermostable serum, was used to demonstrate, by means of a high "neutralization point," the presence of the inhibiting antibody in treated ragweed serum. The convalescent sera and the control sera (NH and S) were compared with it for demonstration of possible inhibiting antibodies. Six patients nonsensitive to ragweed were chosen for the experiment. Rows of injections were made in separate sites with 0.1 c.c. of each of the six mixtures, in the serial dilutions, six for each mixture except for the thermostable mixture, which contained ten dilutions (Table I). Forty-eight hours later each site was injected with 0.025 c.c. of ragweed antigen, 1,000 units per cubic centimeter. After twenty minutes the size of the wheal was recorded and a tracing made. Table I shows the typical result, which was obtained with but slight

variations in every case. Fig. 1 presents typical tracings from one of the cases.

As may readily be seen, the neutralization titer for the NH, P, M, SF, and S mixtures ranged approximately between 2,000 and 2,500 units of antigen, while the neutralization point for the thermostable serum was reached only at 7,000 units per cubic centimeter.

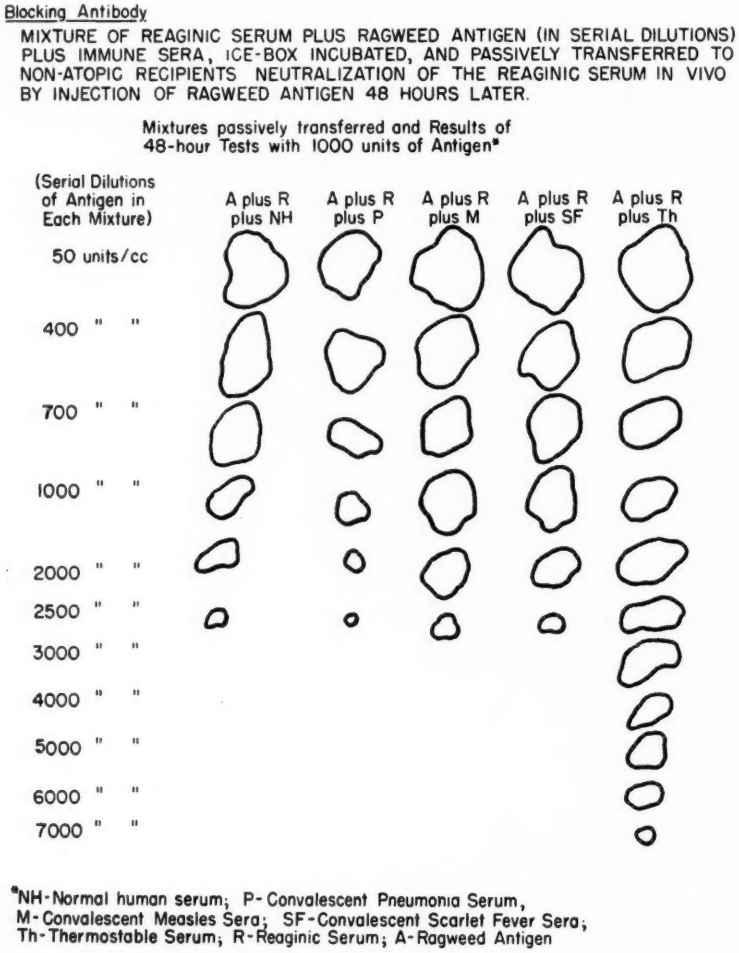
Blocking Antibody
MIXTURE OF REAGINIC SERUM PLUS RAGWEED ANTIGEN (IN SERIAL DILUTIONS) PLUS IMMUNE SERA, ICE-BOX INCUBATED, AND PASSIVELY TRANSFERRED TO NON-ATOPIC RECIPIENTS NEUTRALIZATION OF THE REAGINIC SERUM IN VIVO BY INJECTION OF RAGWEED ANTIGEN 48 HOURS LATER.
Mixtures passively transferred and Results of 48-hour Tests with 1000 units of Antigen*
(Serial Dilutions of Antigen in Each Mixture)
A plus R plus NH
A plus R plus P
A plus R plus M
A plus R plus SF
A plus R plus Th
50 units/cc
400 " "
700 " "
1000 " "
2000 " "
2500 " "
3000 " "
4000 " "
5000 " "
6000 " "
7000 " "
*NH-Normal human serum; P-Convalescent Pneumonia Serum, M-Convalescent Measles Sera; SF-Convalescent Scarlet Fever Sera; Th-Thermostable Serum; R-Reaginic Serum; A-Ragweed Antigen

Fig. 1.

These results indicate (1) that Th serum contained a thermostable antibody capable of inhibiting the combination of antigen and reagin, thus necessitating a greater quantity of antigen to effect neutralization; and (2) that convalescent pneumonia and pooled convalescent measles and scarlet fever sera, like normal serum and saline, contained no such inhibiting substance.

Experiment 2.—Five ragweed-sensitive individuals were injected intradermally with three separate sera: normal nonallergic serum, con-

TABLE I

MIXTURE OF REAGINIC SERUM PLUS RAGWEED ANTIGEN (IN SERIAL DILUTIONS), PLUS IMMUNE SERA, ICEBOX INCUBATED, AND PASSIVELY TRANSFERRED TO NONATOPIC RECIPIENTS. NEUTRALIZATION OF THE REAGINIC SERUM IN VIVO BY INJECTION OF RAGWEED ANTIGEN FORTY-EIGHT HOURS LATER

SERIAL DILUTIONS OF ANTIGEN IN EACH MIXTURE (UNITS PER C.C.)	MIXTURES PASSIVELY TRANSFERRED AND RESULTS OF FORTY-EIGHT-HOUR TESTS WITH 1,000 UNITS OF ANTIGEN					
	A PLUS R PLUS NH	1 A PLUS R PLUS P	2 A PLUS R PLUS M	3 A PLUS R PLUS SF	4 A PLUS R PLUS S	5 A PLUS R PLUS Th.
50	++	++	++	++	+	+++
400	++	++	+	+++	+	++
700	+	+	+	++	+	++
1,000	+	+	+	+	+	+
2,000	±	±	+	±	+	+
2,500	Neg.	Neg.	±	Neg.	Neg.	+
3,000						+
4,000						+
5,000						+
6,000						+
7,000						±

NH, Normal human serum; P, convalescent pneumonia serum; M, convalescent measles sera; SF, convalescent scarlet fever sera; S, physiologic saline; Th, thermostable serum; R, reaginic serum; A, ragweed antigen.

TABLE II

REACTION OF RAGWEED-SENSITIVE SKIN SITES TO RAGWEED ANTIGEN (IN SERIAL DILUTIONS) AFTER INTRODUCING CONVALESCENT SERA INTO THE SAME SITES

RAGWEED ANTIGEN (UNITS PER C.C.)	CONVALESCENT SERUM		NORMAL HUMAN SERUM	NO SERUM CONTROL
	MEASLES	SCARLET FEVER		
1,000	++++	++++	++++	++++
700	++++	++++	++++	++++
500	++++	++++	++++	++++
300	+++	++++	++++	++++
100	++	++	++++	+++
50	++	++	++	++
10	++	++	++	++

valescent measles serum, and convalescent scarlet fever serum. One-tenth of a cubic centimeter of each was injected into seven separate sites in a row, forming three rows. Forty-eight hours later 0.025 c.c. of ragweed pollen extract in each of the following dilutions was injected into one of the sites for each serum and also into a site not previously treated, forming a fourth row: 1,000 units per cubic centimeter, 700 units per cubic centimeter, 500 units per cubic centimeter, 300 units per cubic centimeter, 50 units per cubic centimeter, and 10 units per cubic centimeter. Table II shows the results obtained in each patient tested. It is evident that no interference with the usual antigen and skin-sensitizing antibody reaction resulted from previous injection of the skin with either convalescent measles or convalescent scarlet fever serum.

DISCUSSION

The results of these experiments reaffirmed the fact that the serum of treated ragweed-sensitive patients contains a heat-resistant substance that is capable of inhibiting the type of reaction that takes place in

passively sensitized skin between the reagin in ragweed-sensitive serum and ragweed antigen. As Loveless put it, this thermostable substance apparently competes with the reagin for the antigen which is present at the site of reaction. It was also observed that convalescent serum obtained from one convalescent pneumonia patient did not contain any such inhibiting substance. Tumpeer and Rubens stated that by the dilution technique the inhibiting effect of convalescent scarlet fever sera was "strongest in stock pools, less strong in fresh pools, and least strong in single serum and fresh pools before Berkefeld filtration and treatment with preservatives." We found on the contrary, that convalescent pooled measles and scarlet fever sera, old, preserved, and filtered through a Berkefeld filter contained no inhibiting substance at all. By the neutralization technique, we could not demonstrate that pooled convalescent measles or scarlet fever sera were capable of increasing the neutralization titer of pooled reaginic sera. Furthermore, it was demonstrated that convalescent sera were incapable of inhibiting the reaction between ragweed antigen and skin-sensitizing antibody in the skin of ragweed-sensitive patients. Obviously these sera did not contain substances capable of attaching themselves to the tissue cells in ragweed sensitive skins and of inhibiting the formation of wheals from the subsequent injection of ragweed antigen, a possibility suggested by the experiments of Hilber.

SUMMARY

1. Our experiments showed that the serum of a ragweed-treated patient contained a thermostable substance which, when mixed with reaginic sera, increased its capacity to neutralize ragweed antigen beyond the titer at which it was capable of neutralizing it in the presence of normal human serum or physiologic saline.

2. Convalescent pneumonia, scarlet fever, and measles sera were not similarly capable of inhibiting the antigen-reagin reaction and thus increasing the neutralization titer.

3. Convalescent measles and scarlet fever sera did not appear to be capable of inhibiting the whealing phenomenon produced by ragweed antigen in ragweed-sensitive skins.

REFERENCES

1. Cooke, R. A., Barnard, J. S., Hebald, S., and Stull, A.: Serological Evidence of Immunity with Co-Existing Sensitization in a Type of Human Allergy (Hay Fever), J. Exper. Med. **62**: 733, 1925.
2. Schmidt, W. M., and Lippard, V. W.: Human Passive Transfer Antibody. III. Serial Titrations on Treated and Untreated Patients with Hay Fever, Am. J. Dis. Child. **56**: 550, 1938.
3. Cooke, R. A., Loveless, M., and Stull, A.: Studies in Immunity in a Type of Human Allergy (Hay Fever); Serologic Response of Nonsensitive Individuals to Pollen Injections, J. Exper. Med. **66**: 689, 1937.
4. Cohen, M. B., and Nelson, T.: A Sheep Antibody Which Blocks the Prausnitz-Küstner Reaction, J. Immunol. **34**: 63, 1938.
5. Loveless, M.: Immunological Studies of Pollinosis. I. The Presence of Two Antibodies Related to the Same Pollen-Antigen in the Serum of Treated Hay Fever Patients, J. Immunol. **38**: 25, 1940.

6. Scully, M. A., and Rackemann, F. M.: Studies on the Blocking Antibody of Cooke in the Treatment of Hay Fever, J. ALLERGY **12**: 549, 1941.
7. Tumpeer, I. H., and Rubens, E.: An Inquiry Into Reagins in Convalescent Serum Indicating Its Inhibiting Effect, J. ALLERGY **11**: 333, 1940.
8. Harley, D.: Hay Fever; (I) The Effect of Pollen Therapy on Skin Reactions. (II) Reaction-Inhibiting Substance in Serum of Treated Patients, J. Path. & Bact. **44**: 589, 1937.
9. Langner, P. H., Jr., and Kern, R. A.: Study on the Immunology of Hay Fever; Confirmation of Blocking Substance Formation by Pollen Treatment; Use of Lyophile Serum in Study and Treatment, J. ALLERGY **10**: 1, 1938.
10. Hilber, H.: Local Inhibition of the Tuberculin Reaction by Intracutaneous Injection of Eczema Serum and Its Interpretation, Ztschr. f. Kinderh. **60**: 522, 1939.

DISCUSSION

DR. GELFAND.—Dr. Frank and I felt it important to attack this problem from two angles, since one type of test without the other would have left it only half solved. By the in vitro test we (1) confirmed the findings of Cooke and others—that treated pollen-sensitive serum *does* contain a specific blocking antibody—and (2) showed that this antibody is not influenced in the test tube by the addition of convalescent serum containing other immune substances. By the test in vivo we were able to demonstrate that the skin of a patient who is cutaneously and clinically sensitive to pollen antigen does not alter its reaction because of previous inoculation with sera containing immune antibodies of the bacterial or virus type.

It was of particular interest to find that the so-called thermostable or blocking antibody is specific for each allergen and is not simulated immunologically by bacterial immune substances, either in vitro or in vivo.

DR. HORACE S. BALDWIN, New York, N. Y.—By their search for inhibiting substances in other types of immune sera and their failure to find them, the authors have served to emphasize the specificity of the blocking antibody.

When, in 1935, Cooke, Barnard, Hebald, and Stull described their observations that the serum of some hypersensitive patients following specific therapy acquired the capacity to inhibit the response of passively sensitized skin to the appropriate antigen, the development of an active immunity as a result of the inoculations in hay fever was suggested.

The fact, however, that they as well as Harley concluded that this induced substance did not combine with the antigen and that it acted in some peculiar way other than in the manner of an antibody, which, by definition, unites specifically with the antigen, served to make this whole subject a very puzzling one.

Then in 1940 Loveless published her work which showed the so-called blocking antibody to be thermostable and thus easily separated from the thermolabile reaginic antibody. By means of this separation she showed that the thermostabile antibody is readily induced by inoculation in either sensitive or nonsensitive subjects and combines in a demonstrable and specific way with its antigen. It is therefore a true antibody in the same sense that other antibodies are produced upon injection of an antigen. We do not, therefore, have to think of it as some peculiar brand new type of immune response which occurs only in the atopic individual.

Since it is a specific antibody, one would be surprised if convalescent immune sera, etc., would neutralize it, just as one would be surprised

if diphtheria antitoxin neutralized tetanus toxin, and vice versa. It is just as unreasonable to assume that pneumococcus III antiserum would protect against pneumococcus II.

It is, of course, true that a certain amount of nonspecific antibodies may be found in a wide variety of substances; this, however, does not weaken the fundamental immunologic principle that antibodies are specific for their antigens and vice versa.

The whole question of the thermostable antibody and its relation to the rationale of therapy in hay fever is so important that I am very glad that Dr. Frank and Dr. Gelfand have contributed this paper for us to hear today.

DR. FRANCIS M. RACKEMANN, Boston.—I would like to ask Dr. Frank if he can show any correlation between the amount of blocking antibody and the clinical relief which the patient experienced.

DR. FRANK.—I want to thank Dr. Baldwin for discussing the paper. There is no particular comment on that. But answering Dr. Rackemann's question, we have a series of cases this year which we are studying, with particular respect to what you have just asked, the relationship between the amount of blocking antibody and the clinical results obtained.

I was particularly, I may say, incited to study this question by your own report on the subject last year, in which you noted there was no particular correlation, and I have also noted that Dr. Cooke said there was no particular correlation, whereas Dr. Loveless in her first report shows there was some correlation, although in looking over her results there was not, shall we say, a parallel correlation.

There was one interesting feature about Dr. Loveless' report, however, which is interesting and which has induced us to continue this study a bit further. Very few of the patients which she reported had received a great deal of pollen therapy. I think one had received 56,000 total units, a few about 28,000, and several around 10,000 total dosage, We considered that rather low.

We expect to treat most of our patients with a lot of ragweed antigen, getting their dosage up to 60,000 or more and find not only whether there is a correlation between the amount of blocking antibody and clinical results but whether there is any correlation between the amount of blocking antibody produced as a direct result of the amount of antigen given; in other words, whether there is more blocking antibody the more antigen given.

A COMPARISON OF THE SODIUM AND POTASSIUM METABOLISM OF ASTHMATIC AND NONALLERGIC CHILDREN

PAUL B. DONOVAN, PH.D., AND GEORGE F. HARSH, M.D.
SAN DIEGO, CALIF.

WE HAVE previously reported[1] the effect of large variations in sodium and potassium intake on the incidence, duration, and severity of asthmatic attacks in a group of asthmatic children living together in a local Children's Home. Concurrently with that study, we also compared the sodium, potassium, and acid-base metabolism of these asthmatic children with that of a comparable group of nonallergic children subjected to the same wide variations in sodium and potassium intake. We did not include the results of this comparison in our previous report, since they were not considered germane to the reported study, but the recent publication of extensive reports[2, 3] on the concentration and distribution of sodium and potassium in the body fluids of normal persons suggests that our data may be of sufficient interest to warrant their separate publication. This is especially true since, despite repeated suggestions that allergic symptoms are related to disturbances in sodium and potassium metabolism,[4-7] very little is actually known regarding the concentration and distribution of sodium and potassium in the body fluids of allergic persons.

Objective studies on sodium and potassium metabolism in allergy have been reported in three papers dealing with the concentration of potassium[5] or sodium[8] or both[9] in the serum of allergic patients and a fourth paper[6] dealing with the excretion of sodium in the urine during prolonged asthmatic attacks. In one of these papers,[5] Rusk, Weichselbaum, and Somogyi related serum potassium concentrations to potassium intake, and asthmatic (and other allergic) symptoms to serum potassium concentrations. Stoesser and Cook,[9] on the other hand, observed no relation between either serum potassium or serum sodium concentrations and the intake of these ions, and Donovan and Harsh[8] observed no relation between allergic symptoms and serum sodium concentrations. In the fourth paper,[6] Sheldon, Howes, and Stuart reported that prolonged asthmatic attacks are accompanied by losses of sodium which may exceed the sodium intake by 3 to 5 grams in twenty-four hours. The fragmentary and, in part, contradictory nature of the evidence presented in these reports emphasizes the need for a direct comparison of the sodium and potassium concentrations in the body fluids of allergic and nonallergic persons subjected to the same (known) variations in sodium and potassium intake.

From the Rees-Stealy Medical Research Fund.

The children whose metabolism was compared in the present study included the twelve asthmatics described in the previous report[1] and a group of ten children with negative personal and family histories of allergy who were selected to be, as nearly as practicable, the counterparts of members of the asthmatic group in age, sex, size, weight, and national and racial origin. Both groups were subjected to an extensive preliminary study, by means of both scratch and intracutaneous tests, with a large number of allergens. The asthmatic children were sensitive to a large number of different allergens, some of them previously unsuspected, but the nonallergic children showed consistently negative reactions to the whole series.

After the scratch and intracutaneous tests had been completed and a routine procedure for the study had been established, the children were placed on specially prepared diets selected from foods to which the asthmatic children had shown negative reactions. These foods were prepared in such a way as to preserve a maximum sodium and potassium content. Potassium-rich foods, supplemented by large doses of potassium chloride solution, were served during the first, third and fifth weeks, and sodium-rich foods, supplemented by large doses of sodium chloride solution were served during the second and fourth weeks. The same amount of salt solution was given to each child, but the amount of food eaten, although it was carefully measured, was not restricted and showed considerable variation from child to child and in the same child from day to day.

Since the children were in different classrooms or at other activities which kept them widely scattered during the day, Monday through Friday, it was not practicable to measure their water intake or to collect 24-hour urine specimens during this part of the week without disrupting the routine of the institution. We therefore began each new diet period on Sunday morning, so that the first 24-hour urine specimen on each new diet could be collected, and ended each period with a collection of blood samples on Saturday afternoon. The amount of water ingested was ignored, and only the first morning urine specimens were collected, Tuesday through Saturday.

Urine specimens were collected, measured, and analyzed for pH and titratable acidity as soon as practicable each morning except Sunday. Aliquots of each child's first morning specimens collected during the week were combined and samples of these combined aliquots and of the first 24-hour specimens were analyzed for sodium and potassium. Sodium was estimated by the method of Butler and Tuthill[10] and potassium by the method of Shohl and Bennett.[11]

Blood samples were drawn from the antecubital vein into clean, dry syringes and treated with heparin to prevent coagulation. A portion was sampled immediately for hematocrit and sodium and potassium estimations, and the remainder was promptly centrifuged. After centrifugation, the clear plasma, removed from the cells within half an

hour, was also sampled for sodium and potassium estimations. Sodium and potassium were determined by slight modifications of the methods of Butler and Tuthill[10] and Shohl and Bennett[11] respectively. All analyses were made in duplicate, and the analysis was discarded if the duplicate determinations failed to agree within 2 per cent in the case of sodium, or 3 per cent in the case of potassium. Check solutions, of known sodium and potassium content, were analyzed with each new series of determinations.

Our comparison of the metabolism of the two groups of children included a comparison of (1) their mean daily intake of sodium and potassium; (2) the concentration of sodium and potassium in their whole blood, plasma and red cells; (3) the amount of sodium and potassium excreted in their urine; and (4) the pH, free acid and formol titration of their first 24-hour and subsequent first morning urine specimens on each diet. These parameters were compared statistically by methods described by Fisher,[12] the three periods on a high potassium diet and the two periods on a high sodium diet being treated as single periods. For the sake of economy of space, only the means, standard deviations, differences between the means, and standard error of the differences have been shown in the tables. Differences exceeding twice their standard error,—equivalent approximately to a P value of 0.05,— are considered statistically significant.

TABLE I

MEAN DAILY INGESTION OF POTASSIUM AND SODIUM BY ASTHMATIC AND NONALLERGIC CHILDREN ON DIETS HIGH IN POTASSIUM AND SODIUM RESPECTIVELY

DIET	GROUP	K INGESTED (GM.)		NA INGESTED (GM.)	
		MEAN	DIFF.*	MEAN	DIFF.*
High K	Asthmatic	8.16 ± 1.28	0.03 ± 0.4	1.86 ± 0.47	*0.20 ± 0.098
	Nonallergic	8.19 ± 1.35		1.66 ± 0.26	
High Na	Asthmatic	2.28 ± 0.42	0.18 ± 0.10	4.39 ± 0.45	*0.27 ± 0.12
	Nonallergic	2.10 ± 0.21		4.12 ± 0.29	

*Differences exceeding twice their standard error are considered significant.

The mean daily ingestion of sodium and potassium by each group of children on both diets is shown in Table I. It should be noted that the values refer to grams of sodium and potassium ions and not of sodium and potassium salts. There was no significant difference in the ingestion of potassium by the two groups on either diet, but the asthmatic children ingested a barely significant excess of sodium on both diets. The probability (P) that random sampling would produce equally large differences, lies between 0.02 and 0.05.

The effect of almost a fourfold variation in the mean daily ingestion of potassium on the concentration of potassium in the whole blood and plasma of the two groups is shown in Table II. No significant change took place in either the whole blood or plasma potassium concentrations

of the nonallergic children on either diet. The plasma potassium concentrations of the asthmatic children were significantly higher than those of the nonallergic children on the high sodium diet, and showed a barely significant decrease on the high potassium diet. There also appeared to be an even more significant increase in the red cell potassium concentrations of the asthmatic children on the high potassium diet, but the large probable errors inherent in the calculation of red cell concentrations throw considerable doubt on the validity of this observation.

TABLE II

CONCENTRATION (IN MG. PER CENT) OF POTASSIUM IN BLOOD OF ASTHMATIC AND NONALLERGIC CHILDREN

	GROUP	CONCENTRATION HIGH K DIET MEAN	CONCENTRATION HIGH NA DIET MEAN	DIFFERENCES* HIGH K AND HIGH NA DIETS	
Whole blood	Asthmatic	173.3 ± 11.3	168.7 ± 9.2	4.6 ± 2.9	
	Nonallergic	169.1 ± 7.5	165.0 ± 5.7		4.1 ± 2.3
	(Diff.)	4.2 ± 3.6	(Diff.) 3.7 ± 3.4		
Plasma	Asthmatic	20.7 ± 1.4	21.4 ± 1.0	0.7 ± 0.33	
	Nonallergic	20.4 ± 1.7	20.5 ± 1.6		0.1 ± 0.5
	(Diff.)	0.3 ± 0.4	(Diff.) 0.9 ± 0.4		
Cells†	Asthmatic	370 ± 18.1	355 ± 22.7	15.0 ± 5.6	
	Nonallergic	364 ± 15.0	356 ± 12.0		8.0 ± 4.3
	(Diff.)	6.0 ± 4.6	(Diff.) 1.0 ± 5.9		

*Differences exceeding twice their standard error are considered significant.

†Cell concentrations were calculated from blood and plasma concentrations and relative cell volume as determined by hematocrit.

TABLE III

CONCENTRATION (IN MG. PER CENT) OF SODIUM IN BLOOD OF ASTHMATIC AND NONALLERGIC CHILDREN

	GROUP	CONCENTRATION HIGH K DIET MEAN	CONCENTRATION HIGH NA DIET MEAN	DIFFERENCES* HIGH K AND HIGH NA DIETS	
Whole blood	Asthmatic	198.8 ± 7.5	201.3 ± 7.4	2.5 ± 2.0	
	Nonallergic	202.3 ± 9.4	208.0 ± 8.5		5.7 ± 2.7
	(Diff.)	3.5 ± 2.0	(Diff.) 6.7 ± 3.2		
Plasma	Asthmatic	321.9 ± 7.9	330.3 ± 9.1	8.4 ± 2.3	
	Nonallergic	323.5 ± 8.4	335.6 ± 6.8		12.1 ± 2.4
	(Diff.)	1.6 ± 2.2	(Diff.) 5.3 ± 2.6		
Cells†	Asthmatic	48.0 ± 10.5	33.5 ± 7.6	14.5 ± 2.6	
	Nonallergic	46.4 ± 3.3	41.7 ± 3.1		4.7 ± 1.0
	(Diff.)	1.6 ± 2.1	(Diff.) 8.2 ± 2.0		

*Differences exceeding twice their standard error are considered significant.

†Cell concentrations were calculated from blood and plasma concentrations and relative cell volume as determined by hematocrit. Naturally they are not so accurate as the directly determined concentrations.

In contrast to the situation regarding the potassium concentrations, both groups showed increases in plasma and decreases in red cell sodium concentrations on the high sodium diet. This is shown in Table III. The difference in the decrease of red cell sodium concentrations shown by the two groups on the high sodium diet may not mean a great deal,

but it is notable that the nonallergic children, despite a lower sodium intake, showed a higher plasma sodium concentration on the high sodium diet than did the asthmatic children.

TABLE IV

VOLUME AND SODIUM AND POTASSIUM CONTENT OF URINE EXCRETED BY ASTHMATIC AND NONALLERGIC CHILDREN ON HIGH K AND HIGH NA DIETS

URINE	GROUP	VOL. (C.C.)	DIFF.	CONC'N OF K (MG. %)	DIFF.	CONC'N OF NA (MG. %)	DIFF.
High K Diet							
First 24 hr.	Asthmatic	1320 ± 440		359 ± 123		246 ± 104	
			--------		-------		68 ± 31
	Nonallergic	1330 ± 610		354 ± 120		178 ± 61	
First morning	Asthmatic	210 ± 24		389 ± 104		202 ± 50	
			16 ± 6.1		36 ± 24		41 ± 12
	Nonallergic	226 ± 24		353 ± 74		161 ± 37	
High Na Diet							
First 24 hr.	Asthmatic	1030 ± 440		204 ± 97		404 ± 125	
			330 ± 35		15 ± 43		36 ± 47
	Nonallergic	700 ± 185		219 ± 96		368 ± 81	
First morning	Asthmatic	176 ± 36		203 ± 49		446 ± 54	
			16 ± 12.7		*29 ± 14		*33 ± 16
	Nonallergic	160 ± 23		174 ± 40		413 ± 42	

*Differences exceeding twice their standard error are considered significant.

A probable explanation of this apparent contradiction is contained in Table IV, which shows that the asthmatic children excreted significantly more sodium in the urine on both diets than did the nonallergic children. On the high potassium diet, both groups excreted approximately the same volume of urine, but the concentration of sodium was significantly greater in the urine of the asthmatic children; on the high sodium diet, the concentration of sodium in the urine of the two groups was approximately the same, but the asthmatic children excreted some 40 per cent more urine.

Since it has been suggested that asthma is associated with a mild alkalosis,[13] we attempted to get what information we could concerning the acid-base metabolism of these children by measuring the pH and titratable acidity of their urine specimens. The pH values were measured on untreated samples with a LaMotte urine pH outfit, and the titrations,—free acid and formol titration,—were made on samples treated with neutral oxalate. The results are summarized in Table V.

The pH values of the first 24-hour specimens on the high potassium diet were significantly greater than those of the first 24-hour specimens on the high sodium diet or than those of the first morning specimens on either diet. This was true for both groups of children, but the asthmatic children excreted urine with a lower pH in both the first 24-hour and first morning specimens on the high potassium diet. There was no difference in the pH values of either the first 24-hour or first morning specimens of the two groups on the high sodium diet.

TABLE V

PH AND TITRATABLE ACIDITY OF URINE EXCRETED BY ASTHMATIC AND NONALLERGIC CHILDREN ON DIETS HIGH IN POTASSIUM AND SODIUM RESPECTIVELY

URINE	GROUP	PH		FREE ACID (C.C. N/10 ACID)		FORMOL TITRATION (C.C. N/10 ACID)	
		MEAN	DIFF.	MEAN	DIFF.	MEAN	DIFF.
High K Diet							
First 24 hr.	Asthmatic	6.2 ± 0.5	0.5 ± 0.13	225 ± 154	65 ± 33	383 ± 304	26 ± 71
	Nonallergic	6.7 ± 0.4		160 ± 70		360 ± 299	
First morning	Asthmatic	5.4 ± 0.3	0.2 ± 0.09	81 ± 20	3 ± 5	78 ± 27	6 ± 5.5
	Nonallergic	5.6 ± 0.4		78 ± 19		84 ± 18	
High Na Diet							
First 24 hr.	Asthmatic	5.8 ± 0.6	0.1 ± 0.2	335 ± 148	68 ± 41	311 ± 101	14 ± 34
	Nonallergic	5.9 ± 0.7		267 ± 88		297 ± 124	
First morning	Asthmatic	5.7 ± 0.5	--------	53 ± 16	5 ± 4	51 ± 14	7 ± 4
	Nonallergic	5.7 ± 0.4		48 ± 10		58 ± 15	

Differences Due to Diet

PH	FREE ACID	FORMOL TITRATION
6.2 − 5.8 = 0.4 ± 0.16	335 − 225 = 110 ± 41	386 − 311 = 75 ± 68
6.7 − 5.9 = 0.8 ± 0.16	267 − 160 = 107 ± 25	360 − 297 = 63 ± 56
5.7 − 5.4 = 0.3 ± 0.1	81 − 53 = 28 ± 5	78 − 51 = 27 ± 5.6
5.7 − 5.6 = 0.1 ± 0.1	78 − 48 = 30 ± 4.7	84 − 58 = 26 ± 5

A probable explanation for the anomalous relative alkalinity of the first 24-hour urine specimens on the high potassium diet is contained in the relatively smaller ratio of free acid to formol titration in these urines. This smaller ratio of free acid to formol titration suggests a greather amount of ammoniacal decomposition, but it does not explain why there should be more decomposition in these specimens. According to our figures, the asthmatic children excreted more titratable acid, with a greater proportion of free acid, on both diets than did the nonallergic children. It is to be regretted that we were not prepared to follow the acid-base balance in the blood of these children since the greater excretion of acid by the asthmatic children suggests that they might have shown a relative alkalosis.

SUMMARY

A comparison of the sodium, potassium and acid-base metabolism of comparable groups of asthmatic and nonallergic children subjected to the same wide variations in sodium and potassium intake showed the following differences:

1. The asthmatic children ingested slightly more sodium than did the nonallergic children on both the high sodium and high potassium diets.

2. The plasma potassium concentration of the asthmatic children on the high sodium diet was slightly higher than it was on the high potas-

sium diet, and slightly higher than the plasma potassium concentration of the nonallergic children on either diet.

3. The plasma sodium concentration of the asthmatic children on the high sodium diet was slightly lower than that of the nonallergic children despite a slightly greater intake.

4. The asthmatic children excreted more sodium and more acid in the urine on both diets than did the nonallergic children.

REFERENCES

1. Harsh, G. F., and Donovan, P. B.: The Effect of Wide Variations in Potassium and Sodium Intake in Asthmatic Children, J. Allergy **13**: 105, 1942.
2. Macy, Icie G.: Nutrition and Chemical Growth in Childhood, Vol. I: Evaluation, Springfield, Ill., 1942, Chas. C Thomas.
3. Snyder, R., and Katzenelbogen, S.: The Distribution of Sodium, Potassium, Calcium, Magnesium, Inorganic Phosphorus, and Chloride Between the Blood Serum and Cells of Normal Individuals, J. Biol. Chem. **143**: 223, 1942.
4. Bloom, B.: Use of Potassium Salts in Hay Fever, Preliminary Report, J. A. M. A. **111**: 2281, 1938.
5. Rusk, H. A., Weichselbaum, T. E., and Somogyi, M.: Changes in Serum Potassium in Certain Allergic States, J. A. M. A. **112**: 2395, 1939.
6. Sheldon, J., Howes, H., and Stuart, G.: Observations on Total Water and Sodium Exchanges in Asthmatic Patients, J. Allergy **11**: 1, 1939.
7. Stoesser, A. V., and Cook, M. M.: Electrolyte Exchange in Bronchial Asthma, J. Allergy **11**: 65, 1939.
8. Donovan, P. B., and Harsh, G. F.: Note on Serum Sodium Concentrations of Allergic and Nonallergic Persons, J. Allergy **11**: 567, 1940.
9. Stoesser, A. V., and Cook, M. M.: Possible Relation Between Electrolyte Balance and Bronchial Asthma, Am. J. Dis. Child. **60**: 1252, 1940.
10. Butler, A. M., and Tuthill, E.: An Application of the Uranyl Zinc Acetate Method for the Determination of Sodium in Biological Material, J. Biol. Chem. **93**: 171, 1931.
11. Shohl, A. T., and Bennett, H. B.: A Micro Method for the Determination of Potassium as Iodoplatinate, J. Biol. Chem. **78**: 643, 1928.
12. Fisher, R. A.: Statistical Methods for Research Workers, ed. 7, London, 1938, Oliver & Boyd.
13. Vallery-Radot, Pasteur, et al.: Role of Acid-Base Equilibrium in Certain Eczemas, Urticarias, and Edemas; Case of Provocation at Will of Asthma or Urticaria by Modification of Acid-Base Equilibrium, Bull. et mém. Soc. méd. d. hôp. de Paris **53**: 390, 1937.

OBSERVATIONS ON THE WELTMANN REACTION IN HAY FEVER AND ASTHMA

FRANK F. FURSTENBERG, M.D., AND SIDNEY SCHERLIS,* M.D.
BALTIMORE, MD.

IN 1920 Weltmann[1] devised a serum coagulation test which he thought would be of use in differentiating between proliferative and exudative processes. This test was based upon earlier observations of others that human blood serum will coagulate at different temperatures in different diseases. Weltmann found that the coagulation temperature was influenced by the addition of electrolytes before heating. Less added electrolyte was required to produce heat coagulation of the serum of patients with cirrhosis of the liver than that of normal persons. By varying the amount of electrolyte added, the serum coagulation test, which is known as the Weltmann reaction, was devised.

In the standard procedure, 0.1 ml. of unhemolyzed blood serum is added to each of ten test tubes containing 5 ml. of varying concentrations of calcium chloride arranged as in Table I.

TABLE I

TUBE NO.	CONCENTRATION (%)
1	0.10
2	0.09
3	0.08
4	0.07
5	0.06
6	0.05
7	0.04
8	0.03
9	0.02
10	0.01

These tubes are then heated in boiling water for fifteen minutes, after which the test is read. The coagulation band (C.B.) is determined by the number of tubes in which evident flocculation occurs; mere turbidity is not considered positive. Normally, coagulation occurs in the first six or seven tubes, and the normal coagulation band is 6 or 7 (C.B. = 7) (C.B. = 6). Coagulation always occurs first in the tubes of higher concentration of electrolyte. The coagulation band is considered shortened, "shift to the left," when coagulation takes place in less than six tubes. Coagulation occurring in more than seven tubes is known as a "shift to the right," or a lengthening of the C.B. Shortening of the coagulation band was found in exudative conditions, such as lobar pneumonia and acute febrile diseases, while in proliferative

*From the Protein Clinic, Department of Medicine, Johns Hopkins Hospital.

conditions such as chronic fibrotic tuberculosis, the coagulation band was found to be lengthened. Marked congestive heart failure and cirrhosis of the liver are characterized by a shift to the right.

This test has been used in the study of malignant disease,[2] syphilis,[3] typhoid fever,[4] kidney disease,[5] parenchymatous liver disease,[6] and other conditions. Like the Takata-Ara test, the Hanger cephalin flocculation test, the formol-gel test, and the erythrocyte sedimentation rate, the serum coagulation test has been considered nonspecific and empirical. Unlike the others, however, the Weltmann reaction is used in an attempt to differentiate between exudative and proliferative processes. If this application is a correct one, the test should be of use in the study of allergic conditions and in following the clinical courses of patients with known allergic diseases. It was in order to evaluate the usefulness of this procedure in certain allergic states that the present investigation was carried out.

PLAN OF STUDY

This report is based on the study of fifty-eight patients who were seen in the Allergy Clinic of the Johns Hopkins Hospital between February, 1941, and June, 1942. These patients were seen at appropriate intervals, when symptomatic and symptom free, and both prior to and during treatment periods. They were questioned carefully at each visit by the same observer, and the results noted, after which 5 ml. of whole blood were withdrawn from the patient's antecubital vein for the Weltmann test to be carried out. The cases studied were classified as in Table II.

TABLE II

DISTRIBUTION OF CASES

	NUMBER OF CASES	GROUP NO.
1. Extrinsic allergic conditions	49	
A. Simple seasonal hay fever	18	
Ragweed	11	
Grass and ragweed	5	1
Grass	1	
Tree, grass, ragweed	1	
B. Seasonal hay fever with asthma	9	
Ragweed	8	2
Tree, grass, ragweed	1	
C. Allergic perennial rhinitis and perennial asthma, pollen and inhalant	15	3
D. Bronchial asthma, perennial, pollen and inhalant	7	4
2. Intrinsic allergic conditions	9	
A. Bronchial asthma and perennial rhinitis of unknown origin	9	5

RESULTS

There were 298 Weltmann tests carried out on the entire group. In considering the results, the findings in each of the subgroups will be analyzed, in an attempt to evaluate seasonal changes and the influence

of treatment. Emphasis will be placed only upon the significance of a shortened coagulation band (i.e., a shift to the left) as compared with the normal coagulation band of 6 or 7, or with the patients' usual coagulation band. Thus, only coagulation bands of 5 or less will be considered definitely abnormal. A coagulation band of 6 or 7 is generally considered normal. We have been unable to attach any significance to a prolongation of the coagulation band in studying these patients, and no attempt to evaluate cases in which a shift to the right occurred will be made at this time.

Group 1. Simple Seasonal Hay Fever.—There were eighteen patients in this group, on whom eighty-three Weltmann reactions were obtained. Eleven of this group had ragweed hay fever; 5, grass and ragweed; 1, grass hay fever alone; and 1, tree, grass, and ragweed hay fever. The distribution of these tests is shown in Table III.

TABLE III

C.B.	NUMBER OF TESTS
1	0
2	0
3	0
4	2
5	7
6	24
7	27
8	20
9	3
10	0

The nine coagulation bands below 6 were found in seven patients (Table IV).

TABLE IV

CASE NO.	C.B.	REMARKS
1	5	Shift from C.B. of 6 during season, symptomatic
	5	Shift from C.B. of 6 out of season, asymptomatic
2	5	Shift during season, symptomatic
	5	Shift out of season, asymptomatic
3	5	Shift during season, symptomatic
4	5	Shift during season, symptomatic
5	5	Shift during season, symptomatic
6	4	Shift during season, symptomatic
7	4	Shift during season, asymptomatic

There was no significant change in the coagulation band after a year's treatment in the fourteen patients who were adequately treated and frequently seen. Of these, ten had a shorter coagulation band during season and when symptomatic, than out of season, though not necessarily a coagulation band below 6. In addition to these ten, two other patients had a shorter coagulation band in season than out, making a total of twelve of sixteen patients showing a shift in coagulation band to the left during the season. Only one patient had no decrease in the Weltmann reaction when symptomatic.

Thus, the general tendency in this group was to have a drop in the usual coagulation band, though not necessarily to absolutely abnormal levels, during the period of clinical symptoms. The high incidence (twenty-three out of a total of eighty-three) of moderately prolonged coagulation bands, that is, a coagulation band of 8 or 9, should be noted in this group.

Group 2. Simple Seasonal Hay Fever With Asthma.—In this group of nine patients, eight had ragweed hay fever and asthma, and one had tree, grass, and ragweed hay fever and asthma. The forty Weltmann tests in this group were distributed as shown in Table V.

TABLE V

C.B.	NUMBER OF TESTS
1	0
2	0
3	0
4	0
5	4
6	10
7	19
8	7
9	0
10	0

The four coagulation bands below 6 were noted in three patients (Table VI).

TABLE VI

CASE NO.	C.B.	REMARKS
19	5	During hay fever season, symptomatic
	5	During attack of poison ivy
20	5	During hay fever season, moderately severe hay fever without asthma
21	5	Out of season, symptomatic

No significant change was noted with treatment in the six patients who were receiving adequate perennial treatment and who had frequent Weltmann tests throughout the year. However, these six patients had a decrease in their usual coagulation band during season as contrasted to their normal band in the absence of symptoms.

TABLE VII

C.B.	NUMBER OF TESTS
1	0
2	0
3	1
4	4
5	6
6	30
7	30
8	14
9	0
10	0

Group 3. Allergic Perennial Rhinitis and Asthma.—There were fifteen patients in this group, from whom eighty-five Weltmann tests were obtained. The distribution is shown in Table VII.

The coagulation bands below 6, noted in five patients, are listed in Table VIII.

TABLE VIII

CASE NO.	C.B.	REMARKS
28	5	Asymptomatic
29	5	Asymptomatic
30	5	Hay fever, asthma; symptoms at other times with normal C.B.
31	5	Asthma; this patient had a normal C.B. when asthma was present at other times
32	5	Ragweed asthma, during season
33	4	Asthma; but a normal C.B. with asthma at other times
34	4	Asthma, but a normal C.B. with asthma at other times
35	4	Asthma
	3	Normal, asymptomatic
36	4	Normal, asymptomatic
	5	Normal, asymptomatic

No change in the coagulation band was noted in these fifteen patients with treatment. No consistent change in the coagulation band was associated with the presence or absence of symptoms in individual patients, although six of the eleven low coagulation bands were obtained when symptoms were present.

Group 4. Perennial Allergic Asthma.—In this group of seven patients, there were thirty-seven Weltmann tests, distributed as in Table IX.

TABLE IX

C.B.	NUMBER OF TESTS
1	0
2	0
3	0
4	3
5	2
6	12
7	16
8	3
9	1
10	0

The five coagulation bands under 6 are listed in Table X.

TABLE X

CASE NO.	C.B.	REMARKS
43	5	Normal, asymptomatic
44	5	Normal, asymptomatic
45	4	Normal, asymptomatic
	4	Normal, asymptomatic
46	4	Asymptomatic, seven and one-half months pregnant

It is evident that in this group there is no correlation between an abnormal coagulation band and the presence or absence of symptoms. Low coagulation bands have been noted in other instances of pregnancy.

Group 5. Intrinsic Asthma and Rhinitis.—This group includes nine cases which were thought to be bacterial or psychogenic in origin and were characterized by chronicity. Six of the patients had chronic bronchitis and emphysema. The three others had chronic rhinitis and minor asthmatic symptoms. The fifty-three Weltmann reactions in this group of nine patients were distributed as in Table XI.

TABLE XI

C.B.	NUMBER OF TESTS
1	0
2	1
3	1
4	2
5	5
6	16
7	20
8	8
9	0
10	0

The nine coagulation bands below 6, noted in four patients, are listed in Table XII.

TABLE XII

CASE NO.	C.B.	REMARKS
50	5	Asymptomatic
51	5	Asymptomatic
52	5	Severe asthma
	4	Asymptomatic, three months later
53	2, 3, 4, 5, 5	Asymptomatic, normal C.B. with severe asthma at other times

In this group also there was no evident correlation between the coagulation band and the clinical state of the patients, for when patients were in status asthmaticus, normal coagulation bands were obtained.

DISCUSSION

In considering this group of patients and the results obtained with the Weltmann reaction, it will be seen that the greatest correlation between a low coagulation band and presence of clinical symptoms was found in the group of patients with simple seasonal hay fever, with or without asthma. In these two groups of twenty-seven patients in all, there were twenty-five on whom the data were sufficient to permit of accurate analysis. Of these twenty-five, eighteen showed a decrease in the usual coagulation band (i.e., a shift to the left) during the period when they were having clinical symptoms. However, this decrease in the coagulation band was not always to levels less than 6. That the coagulation band does become shortened in these patients in the presence

of clinical symptoms is shown by the fact that only one of the entire group had no decrease in the coagulation band when symptoms of hay fever were present. Therefore, if a patient is closely followed, and his usual coagulation band is determined and known to lie within a narrow range, a decrease out of this range may be considered abnormal, *for that patient.*

In other groups (Groups 3, 4, and 5) of patients included in this study, no such correlation was noted.

While the variations in the Weltmann reaction in certain patients are pointed out, the physiologic processes underlying these changes are still to be clarified. Dees[7] from a study of single Weltmann tests in a group of twenty-seven patients indicated that a coagulation band below 6 should suggest the presence of an infectious process in addition to the existing allergic conditions. In the present series, however, based upon repeated Weltmann tests upon the same patients, a low coagulation band in a patient with simple seasonal hay fever and asthma was associated with symptoms of allergy rather than any appreciable infectious process. In the patients with perennial allergic rhinitis and asthma, and those with intrinsic asthma and chronic bronchitis, where infection is as prevalent as in those with hay fever and seasonal asthma, low coagulation bands were not consistently noted. The lack of correlation between a low coagulation band and the presence of clinical symptoms of asthma or of infection in these groups has already been pointed out.

The exact significance and application of Weltmann tests in these patients cannot be determined until more is known concerning that which the Weltmann test actually measures. Scherlis and Levy,[8] in a recent publication, found that the Weltmann serum coagulation test is dependent upon the variations in composition of the serum proteins, particularly the alpha globulin fraction. They state that where the percentage of alpha globulin is high, the coagulation band is short, and where the percentage of alpha globulin is relatively low, the coagulation band is prolonged. Therefore the coagulation band may be a reflection of the changes taking place in the blood proteins and not a specific indicator of any one allergic or infectious state.

We do not feel that at the present time, routine Weltmann reactions are of any great practical clinical value in these patients. However, since this test does reflect changes in the blood proteins, it may be used as a simple method of studying these variations in allergic states.

SUMMARY

1. The results of 298 Weltmann reactions in a group of fifty-eight patients with allergic conditions have been reported.

2. The value of these tests in patients with seasonal hay fever and asthma has been indicated.

REFERENCES

1. Weltmann, Oskar: Uber die Spiegelung exsudativ-entzündlicher und fibroser Vorgange im Blutserum, Med. Klin. **26:** 240, 1930.
2. Cairns, A. B., Brandenstein, L.: The Weltmann Reaction in Malignant Disease; Texas State J. Med. **36:** 22, 1940.
3. Balan, E.: Das Koagulationsband von Weltmann bei Syphilis; Arch. F. Dermat. u. Syph. **173:** 483, 1936.
4. Gavrila, J. and Olaru: La reaction de coagulation de Weltmann dans la fievre typhoids; Compt. rend. Soc. de biol. **133:** 303, 1940.
5. Teufl, R.: Der diagnostische Wert der Serumkoagulation nach Weltmann; Wien, Arch. f. inn. Med., **29:** 37, 1936.
6. Kraemer, M.: The Weltmann Test in Diseases of the Liver: Am. J. Digest. Dis. **2:** 14, 1935.
7. Dees, S.: The Value of the Weltmann Serum Coagulation Reaction in Allergic Disease, South. M. J. **34:** 586, 1941.
8. Scherlis, S., and Levy, D. S.: Investigation Into the Mechanism of the Weltmann Serum Coagulation Reaction; A Preliminary Report, Bull. Johns Hopkins Hosp. **71:** 24, 1942.

REPEATED BRONCHIAL RELAXATION IN THE TREATMENT OF INTRACTABLE ASTHMA

ALVAN L. BARACH, M.D.
NEW YORK, N. Y.

IN PATIENTS with severe asthma in whom no etiological agent can be discovered, persisting bronchial spasm may result in prolonged suffering and in pathologic damage to the lungs. In some cases complete loss of the response to epinephrine results in status asthmaticus. In other instances intractable bronchial spasm is either incompletely or transiently relieved by hypodermic injection of epinephrine, and chronic pulmonary overdistention produces varying degrees of invalidism.

Many remedies have been used to break up vicious cycles of severe asthma. The purpose of this paper is to present two recent therapeutic procedures which have frequently been found effective in terminating intractable asthma and to suggest in addition a useful principle of treatment of these cases, namely, repeated relaxation of the spastically contractive circular bronchial muscle. The benefit obtained by nonspecific therapy may be temporary but in some patients freedom from asthma has persisted for one to two years without any other form of treatment. The allergic state of the individual is of incontestable importance, but emphasis on this therapeutic approach should not exclude physiologically directed therapy, especially since the latter may be successful in relieving subjective symptoms and also the pathologic consequences of obstructive dyspnea, even without apparent modification of any allergic factor.

HISTORICAL INTRODUCTION AND PHYSIOLOGIC BASIS OF REPEATED BRONCHIAL RELAXATION

The administration of aminophylline and the inhalation of helium-oxygen mixtures constitute two relatively recent effective methods for the treatment of intractable asthma.

In 1895 Askanazy[1] reported that theobromine salts relieved cardiac dyspnea, but it was not until five years ago that Efron,[2] and Herrmann and Aynesworth,[3] independently, found that intravenous administration of aminophylline (theophylline ethylenediamine) was of remarkable value in the treatment of patients who had become refractory to epinephrine. In fully two-thirds of the patients treated by Efron,[2] the intravenous injection of 0.48 Gm. of aminophylline afforded complete relief. Herrmann and Aynesworth[3] reported that practically all cases that had become adrenalin-fast were restored in their capacity to respond to epinephrine by administration of aminophylline. Carr[4] reported a

From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital.

series of twenty-two patients who were given a total of seventy-eight injections of 0.48 Gm. of aminophylline intravenously. In one-half of these cases relief was immediate, while the effect in the remainder was evident within thirty minutes. The duration of freedom from asthma was from one hour to a period of several days. Of fifty-nine injections of aminophylline given to thirty-one patients with acute paroxysms of asthma mentioned by Brown and Blanton,[5] 22 per cent obtained complete relief, 42 per cent moderate relief, 3 per cent slight relief, and 25 per cent no relief. Of seven patients followed by Herrmann and Aynesworth,[3] who had been treated with intravenous injection of aminophylline, a free interval of three months' duration took place in two instances, and of eight months in one case. In nine outpatients who were treated a total of seventeen times, a free interval of three to five months took place in six instances.

The pharmacologic action of aminophylline in bronchial asthma is not entirely clear, but Young and Gilbert[6] performed experiments in the excised lung which suggested that its action was directly on the bronchial musculature, the drug causing a relaxation of the spastically contracted circular muscle, thus re-establishing the normal diameter of the bronchi.

Aminophylline has also been successfully employed in the relief of Cheyne-Stokes dyspnea, and in the treatment of cardiac insufficiency. It is not clear whether there is any direct effect on the medullary respiratory center, but it has been demonstrated by Greene, et al.[7] that a reduction in intrathecal pressure takes place. The venous blood pressure is lowered if it has been previously elevated, and the total volume of blood flow through the pulmonary circulation is increased. Dilatation of the coronary artery as a result of the intravenous administration of theophylline ethylenediamine appears to have been well demonstrated.

The duration of benefit after treatment with aminophylline is of especial interest. Rackemann[8] reports that the injection of one ampoule intravenously on each of two or three evenings may bring the patient out of status asthmaticus. Although the improvement was maintained in some patients for as long as five to eight months after treatment with intravenous injection of aminophylline, in many other of the reported cases the benefit lasted several days only. It has been our experience that *repeated* relaxation of the spastically contracted circular bronchial muscle over a five- to ten-day period was far more apt to result in a prolonged freedom from severe asthma. This opinion has been already derived from the use of repeated inhalations of helium-oxygen mixtures in the treatment of intractable asthma.[9]

Since daily intravenous injections of aminophylline for a period of five to ten days was frequently not convenient, the author employed rectal instillation of 0.5 to 0.6 Gm. of aminophylline in 20 c.c. of water administered by a 10 F catheter and a 20 c.c. syringe.* Efron[2] had

*An inexpensive glass and rubber bulb syringe is made by Becton, Dickinson & Co., Rutherford, N. J.

already remarked that oral administration was ineffectual in the treatment of severe asthma, and that intramuscular injections are impractical because they are apt to produce considerable pain. Our experience verified this opinion, since repeated intramuscular injections of aminophylline caused considerable soreness in the gluteal region. Furthermore, the rectal administration of aminophylline was readily taught to the patient, who gave himself the injection at night, or if need be, night and morning. The relief of asthma is not as sudden as it is by the intravenous route, but in most instances within a period of forty minutes the bronchi are relaxed, without any side effects such as dizziness, which occasionally accompanies intravenous administration. The only undesirable effect we have observed from rectal administration of aminophylline is nausea, and at times vomiting. When this takes place the dose is reduced to 0.4 Gm., either once or twice a day. It may be pointed out that an enema bag and a large tube is generally unsatisfactory for rectal administration since a moderate amount of the solution is lost, and also since repeated use of a big tube may be irritating to the rectal mucosa.

Helium was introduced as a therapeutic gas for the treatment of obstructive dyspnea in 1934.[10] The physical basis for the employment of helium in the presence of obstruction of any part of the respiratory tubal system was reviewed by the author in 1938.[11] It is evident that an increased pressure both in inspiration and expiration becomes necessary for the movement of air past a point of obstruction. Since the velocity of movement of a gas through a constricted orifice is inversely proportional to the square root of the density of the gas, the pressure required for the movement of an 80 per cent helium-20 per cent oxygen mixture is almost one-half that required for air or for pure oxygen. It was pointed out that when obstruction was confined to a limited area the relief obtained was greatest. When obstruction is continued in a linear direction throughout the smaller branches of the bronchial tubes, as in some cases of tracheobronchitis, the relief obtained by breathing a helium-oxygen mixture is less than when the obstruction is confined to a more limited area. This was accounted for by the fact that the viscosity of helium is not essentially different from that of nitrogen. The clinical improvement resulting from administration of helium-oxygen mixtures to patients with asthma, and with obstructive lesions in the larynx, trachea, and bronchi, has been described by the author and others.[12-17]

In a series of 105 cases of obstructive dyspnea due to lesions in the upper air passages encountered during anesthesia, Eversole[18] reported that complete relief was obtained in 55 cases, partial relief in 37, and no relief in 13 cases. There were 5 additional cases in which partial respiratory paralysis occurred during spinal anesthesia, in which the

paralysis was evident by the absence of intercostal activity and the use of the accessory muscles of respiration. The patients were breathing with considerable difficulty. In all of these patients, breathing was said to be much easier when the helium-oxygen mixtures were administered than when either air or pure oxygen was used.

In experimental tracheal obstruction and in one patient with severe asthma, the inhalation of a helium-oxygen mixture was followed by a decrease in the previously pathologically elevated intrapleural pressure during the inspiratory cycle.[19] Graphic recording of the pulmonary ventilation on a high speed drum in patients with severe asthma revealed a swifter and more complete emptying of the lung air when a helium-oxygen mixture was inhaled, especially during expiration.[20] In many instances the volume of breathing was reduced 20 to 30 per cent immediately after the inhalation of a helium-oxygen mixture was substituted for air. It was evident that bronchial relaxation at times followed inhalation of this lighter than air mixture. In most instances the patient observed that breathing was easier during the treatment, and in a small number of patients this subjective improvement persisted after the period of inhalation.

In patients with intractable asthma the interruption of helium-oxygen therapy was generally followed by a return of severe difficult breathing. Helium-oxygen therapy was therefore at first administered continuously for a period of two to five days in order to keep the patient free from dyspnea the major part of the time. It was later observed, however, that the repeated inhalation of helium-oxygen mixtures for one to two hours, once to three times a day, was frequently followed by a gradual and progressive restoration of epinephrine sensitivity, and a state of mild or no asthma at the end of a five-day period of treatment.[14, 16] In the patient with exceptionally severe asthma, the inhalation of a helium-oxygen mixture has been found far more effective when employed with a positive pressure of 2 to 6 cm. of water in a specially constructed helmet which fits over the head and makes closure at the neck.[21] It has been shown experimentally and clinically that the negative pressure in the intrapleural space is considerably reduced by inhaling atmospheres under positive pressure.[19] Not only is the inspiratory effort much diminished, but the egress of air during expiration is improved, because the intrathoracic bronchioles are maintained at a larger lumen when expiration is conducted under positive pressure.[22] A roentgenographic lipiodol study of patients with asthma showed that the lumina of the smaller bronchi were definitely larger when respiration was conducted under the positive pressure than under normal atmospheric pressure.[23]

Summarizing the results in 84 previously reported cases of status asthmaticus and intractable asthma,[9, 14] the repeated inhalation of helium-oxygen mixtures was followed by either complete freedom from asthma, or very mild asthma, in 40 cases; in 36 cases, an unquestionable

alleviation of the symptoms of asthma took place, with restoration of sensitiveness to epinephrine but with a mild or moderate degree of persisting asthma. In 8 cases, the improvement was either very slight or transient. Of 30 patients in whom follow-up observations were satisfactory, 15 maintained either all or a substantial part of their improvement for six months or more. The conclusion was reached that 90 per cent of the 84 patients with severe intractable asthma were decisively benefited by a program of helium-oxygen therapy. The mechanism of improvement may be further commented upon.

During the period of inhalation of a helium-oxygen mixture there is less pressure on the bronchial wall as a result of the easier entrance and exit of the light gas mixtures. When positive pressure is used for the transport of oxygen (or oxygen and helium) in and out of the lungs, the pressure relationships in the intrathoracic bronchi are decisively changed. An increased positive pressure is then present in the lumina of the entire tracheobronchial tree, as positive pressure forces the atmosphere into the lungs. The intrathoracic bronchi under these circumstances are not subjected to the high negative pressure which was formerly exerted on them. Since the mucous membrane in the smaller bronchioles is no longer exposed to a heightened negative pressure during the respiratory cycle, there is opportunity for absorption of edema. It has been the observation of the author that mucus very frequently *follows* an attack of bronchial spasm; the production of mucus in asthma may be in part linked to the exposure of the bronchial lumina to a maintained negative pressure, which exerts a suction effect on the mucosa.

One of the benefits of maintaining a less effortful type of breathing by inhalation of helium with oxygen, with or without positive pressure, is a general feeling of relaxation which is noticed by the patient as relief of dyspnea. It is thought likely that the improvement in breathing is registered in the central nervous system in such a way as to initiate efferent impulses from the cerebrum that result in bronchial relaxation. Subjective relief of dyspnea from any cause is inevitably followed by a more relaxed state in the patient. This was dramatically shown in the first helium-treated patient, who, after two minutes of inhaling a helium-oxygen mixture, went off into a deep and profound sleep from which it was difficult to arouse him.

The importance of tension in the central nervous system in the maintenance of severe bronchial spasm is illustrated by the frequent beneficial response to injection of morphine or its derivatives. In the author's experience, dilaudid is of special value in the treatment of severe asthma or asthma accompanied by pulmonary emphysema. The relief of asthma from injection of morphine or dilaudid is sometimes spectacular, and when it is repeated for two or three nights may in itself, without any other therapy, terminate the state of intractable asthma. The danger of

giving more than a small dose at one time is that the patient with status asthmaticus may stop respiratory effort and plunge into an asphyxial state. Repeated injection of morphine for the treatment of status asthmaticus is dangerous. The administration of small doses is, however, in certain cases, of very real value and completely justified. Care must be observed in using this drug since patients with very severe asthma have at times become addicts because of the relief afforded by it. For this reason the method of administration of morphine or dilaudid has been frequently altered by the author, the drug being given rectally with the aminophylline solution in most cases.

The point of the present discussion of the use of morphine or its derivatives is to emphasize the role played by the central nervous system in the maintenance of persisting bronchial spasm. A state of general relaxation which is provided by dilaudid is, in some patients, followed by complete disappearance of severe bronchial spasm. It is thought likely that the inhalation of helium-oxygen mixtures, either with positive pressure or without, has an effect on the central nervous system when the dyspnea is totally or even partially relieved. This general relaxation of the patient then ushers in secondary nervous influences that of themselves tend to promote relaxation of the spastically contracted bronchial muscle.

The relaxing effect that comes from central nervous system influences is undoubtedly more apt to be effective when the pathologic physiology in the lungs has been corrected, namely, when the negative pressure in the chest has been reduced, and there is less suction effect on the mucous membranes, when edema in the bronchial mucosa has been lessened, and when pulmonary distention has been reduced by the entrance and exit into poorly ventilated portions of the lungs of the helium-oxygen mixture. The small helium molecule in a helium-oxygen mixture makes possible a more efficient emptying of the lung, and thus a progressive decrease in the pulmonary distention. Since we had observed such favorable results from the inhalation of helium-oxygen mixtures, and since conspicuous relief of status asthmaticus has also been obtained through the intravenous administration of aminophylline, we have combined these two procedures in the treatment of cases of severe intractable asthma. One hundred courses of this combined therapy, over a period of approximately five days, have been administered to a series of seventy-one patients with intractable asthma.

METHODS

The method of treatment varied with the individual case. The patient in severe status asthmaticus was placed continuously in a helium-oxygen hood under a positive pressure of 3 to 5 cm. of water. The majority of the patients who were treated in the hospital were placed in the hood.

In ambulatory patients, including clinic and private patients, helium oxygen mixtures were administered with the meter injector mask.[24-26]

The program of treatment for a patient with intractable asthma admitted to the hospital was as follows:

A rectal injection of 0.5 to 0.6 Gm. of aminophylline in 20 c.c. of water was given immediately. The patient then inhaled the spray of 0.5 c.c. of 1:100 epinephrine, vaporized by a stream of 5 liters per minute of oxygen from a high pressure tank to a nebulizer.* In some instances the inhalation of the epinephrine spray was followed by inhalation of the spray from 1 c.c. of 1 per cent neosynephrin. Hypodermic injection of adrenalin was not used because a refractory state had already taken place. In patients who were very excitable or nervous, a hypodermic injection of 1 or 2 mg. of dilaudid was then given. In some cases, 2 mg. of dilaudid were placed in the aminophylline solution, and administered by rectum. Following the epinephrine spray and administration of aminophylline, the patient was put in the helium-oxygen hood for two hours. The epinephrine spray was repeated in the afternoon, and followed by the helium-oxygen hood for two hours. The nebulizer was used more frequently when it was necessary. In most cases no more helium-oxygen therapy was given that day. In a few very severe patients, an additional two hours was given in the evening. The oxygen concentration was generally set at 25 per cent, but in patients with pulmonary emphysema this was increased to 35 per cent, the remainder helium. A positive pressure of 3 to 4 cm. of water was employed in most cases. In a few patients with severe inspiratory dyspnea the positive pressure was raised to 5 or 6 cm. In the evening before bedtime, a rectal installation of 0.5 or 0.6 Gm. of aminophylline was repeated. In a number of patients to whom dilaudid was not given on admission, it was added to the evening aminophylline mixture. In patients who had persisting severe asthma, dilaudid was added to the evening dose of rectal aminophylline for two, or three, or sometimes four nights.

The combined use of aminophylline by rectum, and helium-oxygen inhalations in the hood twice a day, was kept up for a five-day period, and then abruptly stopped in most instances. In a number of patients, the rectal injection of aminophylline was continued at home after discharge from the hospital, for a period of one to five weeks.

During the period of residence in the hospital, potassium iodide in a saturated solution was given, 1 c.c. three times a day; after discharge, 1 c.c. twice a day for a period of two or three weeks, and then a maintenance dose 1 c.c. every evening before retiring.

Hypodermic injection of adrenalin was dispensed with in the majority of patients. The result of treatment was not considered satisfactory if it was necessary to employ a hypodermic injection of adrenalin. The

*The nebulizer generally used was that made by the Vaponephrin Company, and the form of 1:100 epinephrine employed was that contained in Vaponephrin Solution.

patient was given a nebulizer with 1:100 epinephrine, and instructed to use it if wheezing or a paroxysm of asthma took place. If the asthmatic seizure was so severe as not to be controlled by inhalation of the spray of epinephrine, hypodermic injection of adrenalin was allowed.

In office practice, these patients were given a spray of nebulized 1:100 epinephrine and a rectal injection of 0.5 to 0.6 Gm. of aminophylline, followed by inhalation of a helium-oxygen mixture through the meter mask, the flow of the mixture being set between 7 and 9 liters per minute, for a one-hour period. This was continued for a five-day period, during which time the patient was instructed in the administration of aminophylline by rectum, in order that it might be continued for a period of one to two weeks after the course of office treatment. A tank of 20 per cent oxygen and 80 per cent helium was used, but 1 to 2 liters of oxygen a minute was added through a Y tube to the helium-oxygen mixture, thus increasing the percentage of oxygen in the inspired air to 22 to 25 per cent. In patients who had pulmonary emphysema, the oxygen proportion was increased to 3 or 4 liters a minute, with 7 liters of the helium-oxygen mixture.

The saturated solution of potassium iodide, as well as aminophylline, at times produces nausea. Nausea, and occasionally vomiting, was the only reaction encountered in this regimen. Patients, however, were encouraged to continue with potassium iodide irrespective of nausea; the only basis for discontinuing the iodide which was considered justifiable was the occurrence of a skin rash. Under these circumstances the iodide mixture was stopped until the rash disappeared, and then it was commenced again.

When nausea is severe, it is necessary to reduce the doses of aminophylline so it can be tolerated by the patient. Some individuals can take 0.5 Gm. of aminophylline twice daily without any nausea. If it appears to be desirable to give aminophylline twice a day, the dosage may be very slightly reduced such as 0.4 or 0.45 Gm. of aminophylline. The vast majority of patients can take 0.5 to 0.6 Gm. of aminophylline by rectum once a day without nausea.

In some patients, repeated instillation of rectal aminophylline was given without any other treatment except potassium iodide. This was more apt to be carried out in clinic patients, who were able to treat themselves at home in this way without coming to the hospital or office for helium-oxygen therapy.

RESULTS

The regimen of repeated helium-oxygen inhalation and rectal aminophylline was employed in 26 patients admitted to the hospital. These patients received, in all, 46 courses of therapy lasting approximately five days. There were 45 patients with intractable asthma who were ambulatory and received 54 courses of therapy.

Of the 46 courses of this combined treatment administered to 26 hospital patients, the immediate response to treatment was disappearance of asthma or a very mild residual asthma in 34 instances, a restoration of epinephrine sensitivity with a moderated asthma in 9 instances, and little or no improvement in 3 instances.

TABLE I

THE EFFECT OF HELIUM-OXYGEN AND AMINOPHYLLINE THERAPY IN HOSPITAL AND AMBULATORY PATIENTS WITH INTRACTABLE ASTHMA

NO. OF CASES	TYPE OF CASE	NO. OF COURSES OF THERAPY	IMMEDIATE RESPONSE TO TREATMENT		
			DISAPPEARANCE OF ASTHMA OR VERY MILD SYMPTOMS	RESTORATION OF EPINEPHRINE SENSITIVITY WITH MODERATED ASTHMA	LITTLE OR NO IMPROVEMENT
26	Hospital	46	34	9	3
45	Ambulatory	54	23	17	14
71		100	57 (57%)	26 (26%)	17 (17%)

Of the 54 courses of therapy given to ambulatory patients, there was a disappearance of asthma or very mild symptoms in 23, a restoration of epinephrine sensitivity with persistence of moderate symptoms of asthma in 17, and little or no improvement in 14 instances. It will be observed in Table I that a relatively larger proportion of patients failed to respond in office treatment than of those who were treated in the hospital. This can be readily understood for a number of reasons, the most manifest of them being the larger amount of helium-oxygen therapy given in the hospital, as well as the removal to an environment where complete rest was possible. It should also be pointed out that patients who showed little or no improvement very frequently had varying degrees of pulmonary emphysema. It is noteworthy that 23 of the 54 ambulatory patients were either free from asthma or showed very mild symptoms after a course of five-day treatment in the office, followed by rectal aminophylline at home for a period of one to two weeks.

The total number of patients treated in this way was 71. They were given 100 courses of therapy as outlined above. In 57 an excellent result was obtained, in 26 a good result, and in 17 little or no improvement.

Summarizing the two first groups, there were 83 per cent of patients in which this program of treatment was followed by restoration of epinephrine sensitivity, with either no asthma, or a mild or moderated degree of asthma. In the remainder of cases, 17 per cent of the courses of this type of therapy registered little or no improvement.

The duration of improvement after combined aminophylline and helium-oxygen therapy in hospital and ambulatory patients is shown in Table II. It will be seen that, of 44 courses of therapy administered to 26 hospital cases, the benefit was maintained less than four weeks in

14 instances. In 12 cases either all or a major part of the immediate improvement persisted for between one and four months, in 10 cases for five to twelve months, and in 8 patients one year or more. In 47 courses of combined therapy administered to 31 ambulatory patients, the improvement lasted less than four weeks in 22 cases, in 8 instances one to four months, in 10 cases five to twelve months, and in 7 cases one year or more.

TABLE II

DURATION OF IMPROVEMENT AFTER HELIUM-OXYGEN AND AMINOPHYLLINE THERAPY IN HOSPITAL AND AMBULATORY PATIENTS

NO. OF CASES	TYPE OF CASE	NO. OF COURSES OF THERAPY	MAINTENANCE OF ALL OR A MAJOR PART OF IMMEDIATE IMPROVEMENT			
			1 TO 4 WEEKS	1 TO 4 MONTHS	5 TO 12 MONTHS	1 YEAR OR MORE
26	Hospital	44	14	12	10	8
31	Ambulatory	47	22	8	10	7
57	Total	91	36*	20	20	15

*Many recurrences in this group took place in a relatively small number of cases of severe asthma.

In combined hospital and ambulatory patients there were 91 courses of therapy given to 57 patients. Of the 91 courses improvement persisted less than four weeks in 36 instances, one to four months in 20, five to twelve months in 20, and for one year or more in 15 instances. Of the group in which the relapse took place in less than four weeks, there were many recurrences in a relatively small number of cases of severe asthma. It must be admitted that relapses after a course of treatment are disappointing when they occur within a one-month period of time. The response in the two middle groups, however, in which improvement lasted from one to four months in 20 instances of treatment, and five to twelve months in 20 instances of treatment, appeared to be of decided advantage to both these groups of cases. Most encouraging of all was the finding that 15 of the 91 courses were followed by the maintenance of all or a major part of the immediate improvement for one year or more.

TABLE III

EFFECTS OF RECTAL INJECTIONS OF AMINOPHYLLINE IN AMBULATORY PATIENTS

NO. OF CASES	NO. OF COURSES OF THERAPY	DISAPPEARANCE OF ASTHMA OR VERY MILD SYMPTOMS	RESTORATION OF EPINEPHRINE SENSITIVITY WITH MODERATED ASTHMA	LITTLE OR NO IMPROVEMENT
20	40	8	14	18

The effect of rectal injections of aminophylline without helium-oxygen therapy is shown in Table III. There were 40 courses of rectal aminophylline therapy for a period of three to five days administered to 20 ambulatory patients who had developed more or less severe and intract-

able asthma. In 8 instances the therapy was followed by a disappearance of the asthma or very mild symptoms, in 14 by restoration of epinephrine sensitivity with moderated asthma, and in 18 instances by little or no improvement.

TABLE IV

DURATION OF IMPROVEMENT AFTER RECTAL INJECTIONS OF AMINOPHYLLINE IN AMBULATORY PATIENTS

NO. OF CASES	NO. OF COURSES OF THERAPY	MAINTENANCE OF ALL OR A MAJOR PART OF IMMEDIATE IMPROVEMENT		
		1 TO 4 WEEKS	1 TO 4 MONTHS	6 TO 12 MONTHS
15	25	12	11	2

In Table IV the duration of improvement after rectal injection of aminophylline was followed in 15 patients who had received 25 courses of therapy. In 12 instances the maintenance of all or a major part of the immediate improvement lasted between one and four weeks, in 11 instances the improvement lasted from one to four months, and in 2 instances from six to twelve months. It is evident that the results in this group of ambulatory patients who were given only a course of rectal aminophylline therapy are not as good as in the series treated by combined helium-oxygen and aminophylline therapy, either in the hospital or as ambulatory patients. However, a satisfactory immediate result was obtained in 22 of 40 courses of such therapy, and the improvement was maintained a sufficient length of time to justify employment of this procedure, namely, from one to twelve months in 13 of 25 courses of rectal therapy. The method of rectal installation of aminophylline is so practical for the patient to employ at home that it is considered a valuable adjunct to palliative therapy.

DISCUSSION

Repeated bronchial relaxation has been employed in the treatment of intractable asthma in the belief that a vicious cycle of persisting bronchial spasm may be frequently overcome, and the improvement obtained by this method will be more lasting than by single intravenous injection of aminophylline or other measures employed for the relief of status asthmaticus. Since relaxation of the bronchial wall was the aim of treatment, a summation effect was obtained by the combined use of helium-oxygen therapy and repeated injection of aminophylline. The rectal mode of administration was chosen because it was both effective and feasible in ambulatory, home, and hospital patients. The cautious employment of dilaudid for two to five days, generally in the rectal aminophylline solution, was of unquestionable help in many instances by promoting total relaxation of the central nervous system. The continuous ingestion of potassium iodide in saturated solution was also con-

sidered to be of value both during and after courses of aminophylline and helium-oxygen therapy. The author is in agreement with the following statement:* "Perhaps the most frequently helpful drug in preventing the recurrence of asthma is an iodide, probably because most asthma is due to involvement of the air passages, and this is specifically a stimulant to the mucous membranes of the nose, throat, and bronchial tubes."

The immediate response to combined helium-oxygen and aminophylline therapy in severe intractable asthma is a conspicuous relief of symptoms in the majority of cases, namely, in 83 of 100 cases of such therapy. Of greater significance is the duration of improvement. Of 91 courses of therapy in which an adequate follow-up was possible, a relapse of symptoms took place in 36 instances. Although many recurrences in this group took place in a relatively small number of severe cases, the failure of maintenance of the immediate improvement is disheartening to this group. However, in 40 of the 91 courses of therapy the maintenance of a major part of the immediate improvement for a period of one to twelve months definitely justified its employment. Finally, the fact that 15 of 91 courses of therapy were followed by maintenance of all or a major part of the immediate improvement for more than one year is good reason for using the regimen outlined. It will perhaps seem a more satisfactory result if it is remembered that these 15 excellent results occurred in a total number of 57 patients. In other words, 26 per cent of patients with severe intractable asthma had either no symptoms or very mild symptoms for a period of over one year following combined aminophylline and helium-oxygen therapy. Since all attempts to discover an etiological allergic factor in these cases had been fruitless, the results of a program of repeated bronchial relaxation are considered eminently worthwhile. It would seem likely that a habit of bronchial spasm is broken by this method in the majority of cases of intractable asthma.

In a more recent series of cases not included in this article, the duration of improvement has been lengthened by employing rectal instillation of aminophylline over a far longer period of time than reported above. In patients with intractable asthma in whom functional pulmonary emphysema is marked, instillations of 0.5 Gm. of aminophylline rectally have been maintained for as long as one to three months after the original course. In most cases an evening dose of aminophylline is all that is required.† The physiologic advantage of maintaining a patent bronchial passageway over a longer period of time is an unquestionable progressive amelioration of pulmonary distention. This should be maintained until the patient requires nothing more than inhalation of the nebulized spray of epinephrine solutions.

*Fishbein, Morris, editor: Handbook of Therapy, ed. 11, Chicago, 1937, American Medical Association.

†Colonic ether in olive oil is at times very helpful in completing the program of bronchial relaxation.

SUMMARY

1. Repeated bronchial relaxation was carried out in a series of 71 patients with severe intractable asthma by employing the following procedures:

a. Rectal injection of 0.5 Gm. of aminophylline once or twice daily for a period of one to three weeks.

b. Inhalation of helium-oxygen mixtures for one to six hours daily for a period of five days.

c. The use in some cases, of dilaudid, generally in 2 mg. doses, administered in the rectal aminophylline solution.

d. Continuous ingestion of saturated solution of potassium iodide in doses of 1 to 3 c.c. daily.

e. Inhalation of the nebulized spray of 1:100 epinephrine, and in some instances of 1 per cent neosynephrin, one to five times daily.

2. The summation effect of these procedures to relax the constricted bronchial muscle was employed in 100 courses of therapy administered to 26 hospital and 45 ambulatory patients. The immediate response to treatment was the disappearance of asthma or very mild symptoms in 57 per cent, restoration of epinephrine sensitivity with moderated asthma in 26 per cent, and little or no improvement in 17 per cent. The duration of improvement in 91 courses, administered to a total of 57 patients, was one to four weeks in 36 instances, one to four months in 20 instances, five to twelve months in 20 instances, and one year or more in 15 instances of this therapy.

3. The effect of rectal injection of aminophylline over a period of three to five days without other therapy was tested in 40 courses given to 20 patients. In 8 instances a disappearance of asthma or very mild symptoms took place, in 14 a restoration of epinephrine sensitivity with moderated asthma, and in 18 instances little or no improvement. The duration of improvement after rectal injection of aminophylline in 25 courses, administered to 15 ambulatory cases, was one to four weeks in 12 instances, one to four months in 11 instances, and six to twelve months in 2 instances of this type of therapy.

4. The beneficial results of combined helium-oxygen and aminophylline therapy were excellent to good in 83 per cent of 100 courses, especially in 15 cases, patients in whom little or no symptoms of asthma were present for periods in excess of one year, and in 20 patients in whom the improvement lasted between five and twelve months.

5. Repeated bronchial relaxation by combined aminophylline and helium-oxygen therapy is, therefore, considered an effective measure in terminating intractable asthma in those patients in whom no etiological agent can be discovered.

6. Prolonged rectal aminophylline instillation is indicated for those patients with intractable asthma who have, in addition, marked functional pulmonary emphysema.

REFERENCES

1. Askanazy, S.: S. Klinishes über diuretin, Deutsches Arch. f. klin. Med. **56:** 259, 1895.
2. Efron, B. G.: Status Asthmaticus, by J. S. Kahn, J. Allergy **8:** 163 (Discussion), 1938.
3. Herrmann, G., and Aynesworth, M. B.: Successful Treatment of Persistent Extreme Dyspnea "Status Asthmaticus," J. Lab. & Clin. Med. **23:** 135, 1937.
4. Carr, H. A.: Treatment of Acute Attacks of Bronchial Asthma by Intravenous Injection of Aminophyllin, J. Lab. & Clin. Med. **25:** 1295, 1940.
5. Brown, A. G., III, and Blanton, W. B.: Therapeutic Effects of Aminophyllin in Asthma, South. M. J. **33:** 1184, 1940.
6. Young, R., and Gilbert, R.: The Use of Theophylline With Ethylenediamine (Aminophyllin) for the Control of Bronchial Spasm, J. Allergy **12:** 235, 1941.
7. Greene, J. A., Paul, W. D., and Feller, A. E.: Action of Theophylline With Ethylenediamine on Intrathecal and Venous Pressures in Cardiac Failure and on Bronchial Obstruction in Cardiac Failure and in Bronchial Asthma, J. A. M. A. **109:** 1712, 1937.
8. Rackemann, F. M.: The Pharmacopeia and the Physician; Use of Drugs in Asthma, J. A. M. A. **114:** 1998, 1940.
9. Barach, A. L.: The Therapeutic Use of Helium, J. A. M. A. **107:** 1273, 1936.
10. Barach, A. L.: Use of Helium as a New Therapeutic Gas, Proc. Soc. Exper. Biol. & Med. **32:** 462, 1934.
11. Barach, A. L.: Physiological Methods in the Diagnosis and Treatment of Asthma and Emphysema, Ann. Int. Med. **12:** 454, 1938.
12. Barach, A. L.: Use of Helium in the Treatment of Asthma and Obstructive Lesions in the Larynx and Trachea, Ann. Int. Med. **9:** 739, 1935.
13. Kernan, J. D., and Barach, A. L.: Role of Helium in Cases of Obstructive Lesions in the Trachea and Larynx, Arch. Otolaryng. **26:** 419, 1937.
14. Barach, A. L., and Cromwell, H. A.: Recent Advances in Oxygen and Helium Therapy, With Special Reference to the Treatment of Bronchial Asthma, M. Clin. North America **24:** 621, 1940.
15. Maytum, C. K., Prickman, L. E., and Boothby, W. M.: Use of Helium and Oxygen in the Treatment of Severe Intractable Asthma, Proc. Staff Meet., Mayo Clin. **10:** 785, 1935.
16. Metz, C. W., Wearner, A. A., and Evans, A. E.: Therapeutic Use of Helium, South. M. J. **32:** 34, 1939.
17. Schwartz, A. L.: The Relief of Status Asthmaticus by Helium, J. Med. **19:** 122, 1938.
18. Eversole, U. H.: The Use of Helium in Anesthesia, J. A. M. A. **110:** 878, 1938.
19. Barach, A. L.: Use of Helium in the Treatment of Asthma and Obstructive Lesions in the Larynx and Trachea, Ann. Int. Med. **9:** 739, 1935.
20. Barach, A. L.: Physiological Methods in the Diagnosis and Treatment of Asthma and Emphysema, Ann. Int. Med. **12:** 454, 1938.
21. Barach, A. L.: Recent Advances in Inhalation Therapy in the Treatment of Cardiac and Respiratory Disease; Principles and Methods, New York State J. Med. **37:** 1095, 1937.
22. Barach, A. L., Martin, J., and Eckman, M.: Positive Pressure Respiration and Its Application in the Treatment of Acute Pulmonary Edema, Ann. Int. Med. **12:** 753, 1938.
23. Barach, A. L., and Swenson, P.: Effect of Breathing Gases Under Positive Pressure on Lumens of Small and Medium-Sized Bronchi, Arch. Int. Med. **63:** 946, 1939.
24. Barach, A. L., and Eckman, M.: A Physiologically Controlled Oxygen Mask Apparatus, Anesthesiology **2:** 421, 1941.
25. Barach, A. L., and Eckman, M.: A Mask Apparatus Which Provides High Oxygen Concentrations With Accurate Control of the Percentage of Oxygen in the Inspired Air and Without Accumulation of Carbon Dioxide, J. Aviation Med. **12:** 39, 1941.
26. Barach, A. L., and Molomut, N.: An Oxygen Mask Metered for Positive Pressure, Ann. Int. Med. **17:** 820, 1942.

ROENTGEN OBSERVATIONS ON CHILDREN WITH GASTROINTESTINAL ALLERGY TO FOODS

JOSEPH H. FRIES, M.D., BROOKLYN, N. Y., AND MARVIN MOGIL, M.D., NEW HAVEN, CONN.

THIS communication is an extension of a previous preliminary report[1] dealing with roentgenographic studies of children exhibiting gastrointestinal disturbances resulting from the ingestion of foods to which they were allergic. In order to evaluate this use of the roentgenogram, our observations were continued on a larger group of children. Our previous findings were confirmed. However, with a larger group, it was possible to arrive at an estimation of their frequency. The significance of adulterants in barium test meals became apparent. We were also able to show that the reactions produced were due to the specific allergenic effect of the food and not to its presence in the barium.

Crispin,[2] Christian,[3] and Duke[4] were among the earliest to obtain roentgenologic evidence of the disturbances which occur in allergic reactions of the gastrointestinal tract. Andresen[5] and Gay[6] contributed further observations. Intentional feeding of allergens to induce allergic reactions was employed by Eyermann,[7] Serio,[8] Rowe,[9] Fries and Zizmor,[1] Hansen and Simonson,[10] Hampton,[11] Wing and co-workers,[12] and Cooke.[13]

PROCEDURE

A total of thirty allergic children were studied in the various investigations to be described. These children ranged in age from 4 to 14 years. All had repeatedly exhibited gastrointestinal disturbances within a few minutes after the ingestion of certain foods. The allergic nature of these reactions was confirmed in a majority by cutaneous testing.

Comparative roentgenographic studies, including fluoroscopy, were made. In the control series, a 50 per cent suspension of plain barium sulfate in water was used. In the study with allergen, the antigen was added to the barium mixture in amounts determined by previous clinical trials to be sufficient to produce gastrointestinal symptoms (Table I).

Approximately equal quantities of barium were used in both studies on the same patient. The actual quantity varied with each patient according to age and cooperation. At least one week elapsed between the control and allergen studies. The offending food was added to the meal without the knowledge of the subject in order to minimize psychic factors.

Fluoroscopy was begun as soon as the child had ingested the meal. Roentgenograms were taken immediately thereafter, and again at intervals, usually after one, three, six, twenty-four, and forty-eight hours.

From the Allergy Division of the Jewish Hospital of Brooklyn, N. Y.

TABLE I

AMOUNT OF OFFENDING ALLERGEN EMPLOYED TO INDUCE GASTROINTESTINAL ALLERGIC REACTIONS

NAME	AGE (YR.)	ALLERGEN	AMOUNT
D. S.	6	Egg	½ dram
P. K.	6	Egg	1 dram
W. C.	4	Egg	1 dram
A. K.	7	Egg	4 drams
P. G.	6	Egg	4 drams
J. C.	5	Egg	4 drams
N. L.	11	Egg	6 drams
M. S.	5	Egg	6 drams
M. Lu.	9	Egg	6 drams
R. L.	11	Egg	6 drams
G. T.	8	Egg	6 drams
R. E.	12	Egg	6 drams
J. R.	6	Egg	6 drams
S. F.	5	Egg	6 drams
I. L.	9	Egg	6 drams
S. V.	12	Egg	6 drams
C. L.	3	Egg white	3 drams
D. St.	12	Egg white	10 drams
J. L.	11	Fish	½ dram
A. Kr.	5	Milk	1 ounce
M. V.	9	Milk	1 ounce
A. DeM.	7	Milk	3 ounces
L. S.	6	Nut	1 dram
T. M.	14	Nut	1½ drams
I. S.	11	Nut	2 drams
B. S.	14	Corn	1 ounce
B. F.	8	Wheat	1 dram
D. L.	4	Wheat	1½ drams
R. K.	10	Oats	2 drams
M. C.	7	Cabbage	2 drams

TABLE II

GASTRIC RESPONSES TO ALLERGEN-BARIUM MEAL AS NOTED BY FLUOROSCOPY IN TWENTY-SIX SUBJECTS

	PASSAGE OF ALLERGEN-BARIUM THROUGH PYLORUS		
	DELAYED (19 SUBJECTS)	NORMAL (5 SUBJECTS)	RAPID (2 SUBJECTS)
Gastric Tonus:			
Decreased	13	1	
Normal	4	4	
Increased	2		2
Gastric Peristalsis:			
Decreased	16		
Normal	2	5	
Increased	1		2

OBSERVATIONS ON THE STOMACH

Fluoroscopic.—During the fluoroscopy of twenty-six children, a delay in the passage of allergen-barium from the stomach to the duodenum was observed in nineteen (Table II). In these, allergen-barium did not leave the stomach for from twenty to thirty minutes or longer. Gastric peristalsis was diminished and ineffectual in sixteen subjects. Dilatation, sometimes to excessive degree, was observed in thirteen children. In some instances, allergen-barium entered the small intestine irregu-

larly and intermittently, resulting in the collection of isolated boluses of barium instead of in the usual fine dispersion.

Rapid passage of barium into the duodenum was observed in only two children. In these the stomach emptied completely in less than one-half hour.

These pronounced variations from the normal were usually accompanied by nausea, emesis, or abdominal pain. Five of the twenty-six children exhibited normal emptying of the stomach and experienced no symptoms.

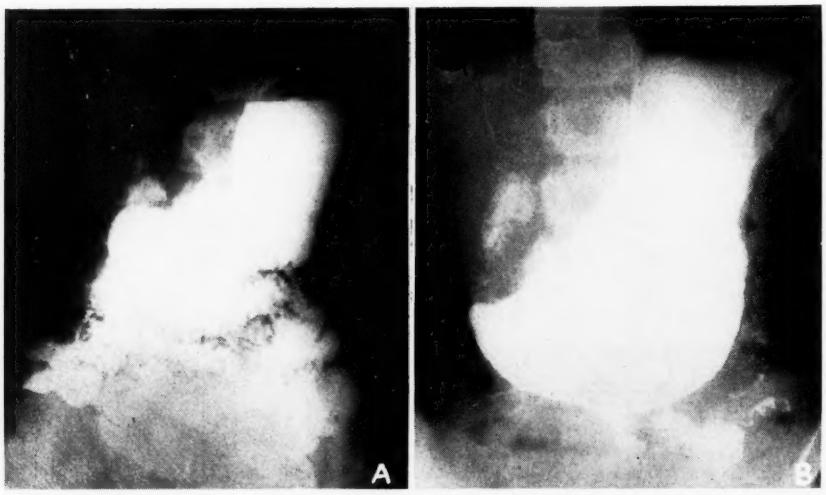

Fig. 1.—Observations twenty minutes after ingestion of meal (R. L.). *A*, Control study (barium meal) shows the free passage of barium into the small intestine. *B*, Allergen study (egg-barium meal) reveals dilatation of the stomach. Note the suggestion of edema of the pyloric region and the boluses in the jejunum.

Roentgenographic.—The immediate roentgenograms usually corroborated the impressions obtained from fluoroscopy. These recorded the patterns of the hypotonic stomach with delayed emptying in nineteen subjects (Fig. 1). Hypertonicity of the stomach associated with accelerated emptying was seen twice (Fig. 4).

Roentgenograms taken at the six-hour period in twenty subjects revealed gastric retention in eleven (Table III). The approximate amount of such retention varied up to 66 per cent, one subject.[1] Two subjects had 50 per cent retention (Figs. 3*B* and 8); two subjects, 33 per cent; three subjects, 25 per cent; and three subjects about 10 to 20 per cent. No retention was observed in nine children. Gastric retention was not observed in the control series with plain barium, except in the case of M. Lu. who had had a previous Ramstedt operation (Fig. 2). Three subjects (L. S., J. C., and G. T.) receiving proprietary barium mixtures instead of plain barium exhibited some retention in both control and allergen series. However, it should be noted that there was even more retention shown in the comparative films for which specific antigen was fed.

OBSERVATIONS ON THE SMALL INTESTINE

Alterations in the small intestinal tract were infrequent, and, when present, seemed to be accompanied by fairly severe symptoms. Of the group of thirty children, increased segmentation was observed in five (Figs. 2 and 3*A*). This segmentation was uniquely illustrated in one child in whom the allergic response was delayed until after the small intestine had filled normally. As the allergic reaction developed, increased tonus became more obvious, while the feathery appearance of the mucosa coarsened. The allergen-barium separated into irregular

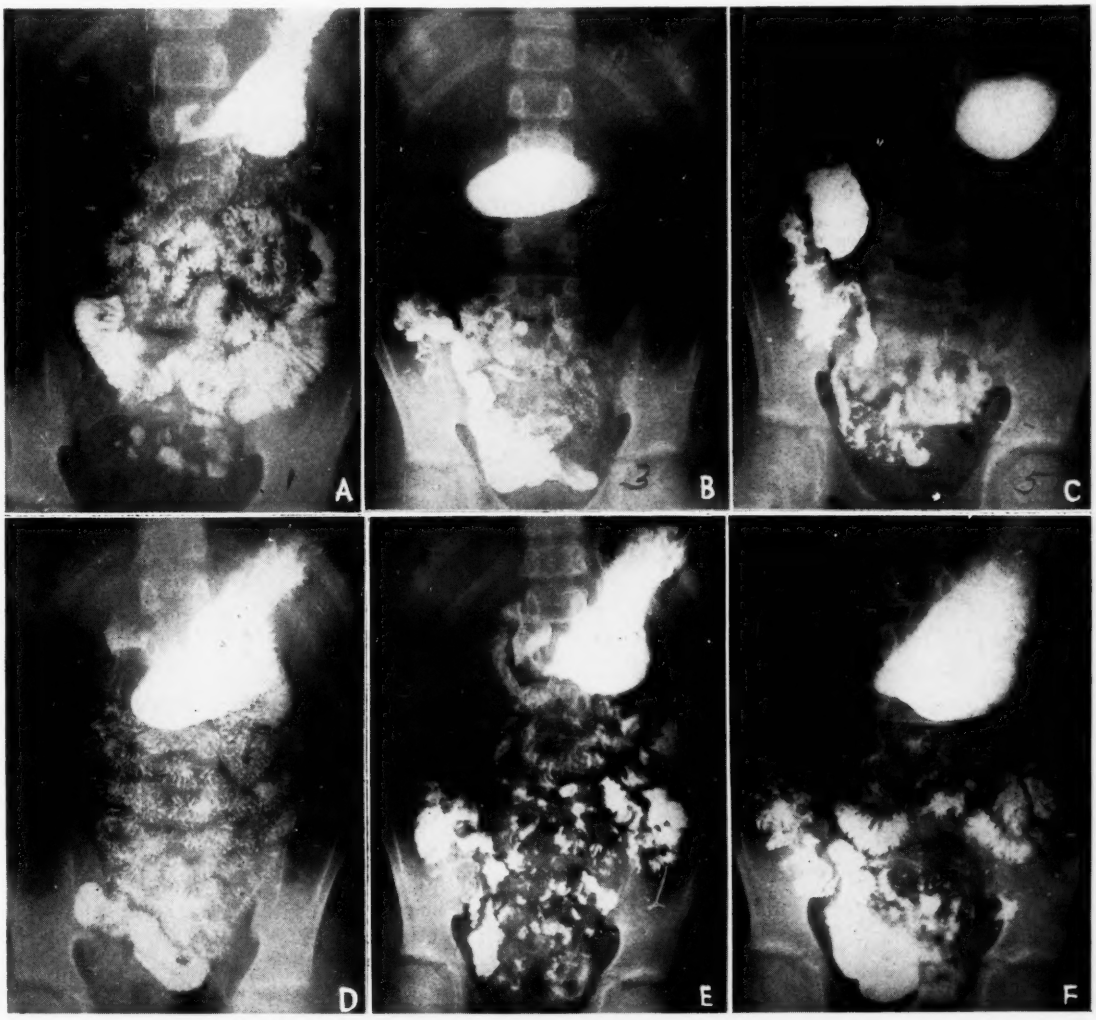

Fig. 2.—A comparison of control (*A*, *B*, *C*) and allergen (egg) series (*D*, *E*, *F*) at the one-, three-, and five-hour periods (M. Lu.). There is no observable difference between the one-hour pictures, the patient being symptom-free. The allergen studies at three and five hours show increased segmentation of the small intestine concomitant with a prolonged attack of severe abdominal pain. Gastric retention is more pronounced with the allergen at five hours. (Patient had Ramstedt operation during infancy.)

TABLE III

A COMPARISON IN TWENTY SUBJECTS OF THE DEGREE OF GASTRIC RETENTION AT SIX HOURS FOLLOWING BARIUM AND ALLERGEN-BARIUM MEALS

NAME	ALLERGEN		CONTROL	
	PER CENT OF GASTRIC RETENTION	PRESENCE OF SYMPTOMS	PER CENT OF GASTRIC RETENTION	PRESENCE OF SYMPTOMS
L. S.	66*	+	15*	–
B. S.	50	+	0	–
I. S.	50	+	0	–
M. Lu.	33†	+	20†	–
T. M.	33	+	0	–
J. C.	25*	+	10*	–
M. C.	25	+	0	–
R. E.	25	+	0	–
A. Kr.	20	+	0	–
B. F.	15	+	0	–
R. L.	15	+	0	–
A. K.	0	+	0	–
D. L.	0	+	0	–
C. L.	0	+	0	–
D. S.	0	+	0	–
G. T.	0*	–	10*	–
N. L.	0	–	0	–
J. L.	0	–	0	–
M. S.	0	–	0	–
P. G.	0	–	0	–

*Proprietary barium mixtures used.
†Ramstedt operation in infancy.

masses which subsequently merged into larger aggregations, giving the impression of localized dilatations (Fig. 2).

In the others the allergic gastrointestinal response was of the immediate type. Whatever allergen-barium issued from the stomach tended to remain in the globular shapes for hours and showed no tendency to dispersion.

One boy exhibited dilatation of the small intestine (Fig. 3*B*).

Accelerated motility was observed in two children, the allergen-barium progressing rapidly through the small intestine and reaching the cecum within an hour (Fig. 4).

OBSERVATIONS ON THE COLON

As the allergen-barium progressed through the colon, there was evidence of hypertonicity of the transverse region in three instances. In these, a narrowed shadow, irregular haustrations, and increased sulci were observed (Figs. 3*B* and 7). One patient had, in addition, a marked narrowing of the descending colon.

At the six-hour period there was little difference in motility between the corresponding studies. Moreover, motility did not appear to be affected by the amount of gastric retention. At twenty-four and forty-eight hours there seemed to be a tendency toward delayed evacuation of the colon in the allergen series.

OBSERVATIONS WITH THE ALLERGEN-BARIUM ENEMA

Seventeen subjects were studied after the rectal administration of barium and allergen-barium mixtures (Table IV). Eleven children showed definite evidences of abnormal reactions shortly after the introduction of the allergen-barium mixture. Constriction of the colon, which was not present in the controls, was observed in ten. In three there was

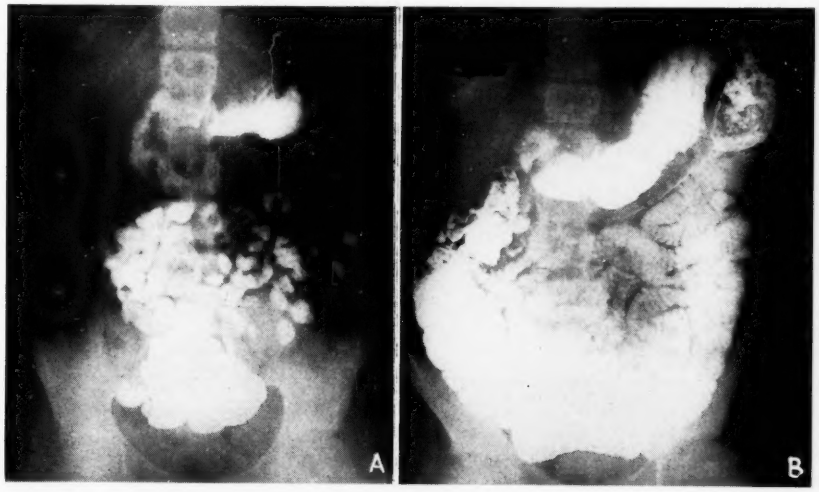

Fig. 3.—Six-hour allergen studies. *A* (R. L.), egg-barium meal; small intestine shows abnormal segmentation. There is a slight gastric residue. *B* (B. S.), corn-barium meal; note the dilatation of the entire small intestine, gastric retention, and marked narrowing of the transverse colon.

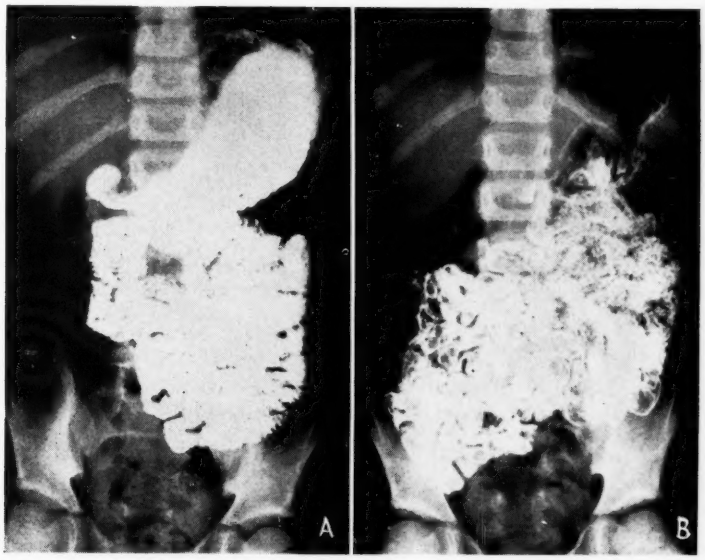

Fig. 4.—One-hour studies (M. S.). *A*, control (barium meal) shows normal rate of emptying from stomach into the small intestine. *B*, Allergen (egg-barium meal) demonstrates hypermotility through the stomach into the small intestine. Note the distribution of barium throughout the small intestine to the cecum by one hour. The stomach has completely emptied.

TABLE IV

SUMMARY OF REACTIONS IN THE COLON TO ENEMAS OF ALLERGEN-BARIUM MIXTURES IN SEVENTEEN SUBJECTS

NAME	ALLERGEN	QUANITY	REGION	REACTION
P. K.	Egg	½ dram	Transverse and descending colon	Constriction
R. E.	Egg	4 drams		
B. F.	Wheat	4 drams		
R. K.	Oats	2 drams	Transverse colon	
M. C.	Cabbage	3 drams		
A. K.	Egg	3 drams		
L. S.	Nut	1 dram		
S. F.	Egg	3 drams		
M. L.	P. B. M.*			
G. T.	Egg	4 drams	Descending colon	
A. De M.	Milk	2 ounces	Entire colon	Dilatation
R. Ls.	Egg	4 drams		None
I. S.	Egg	6 drams		
J. C.	Egg	6 drams		
R. Ly.	Egg	6 drams		
D. S.	Egg white	10 drams		
D. L.	Wheat	2 drams		

*Proprietary barium mixture.

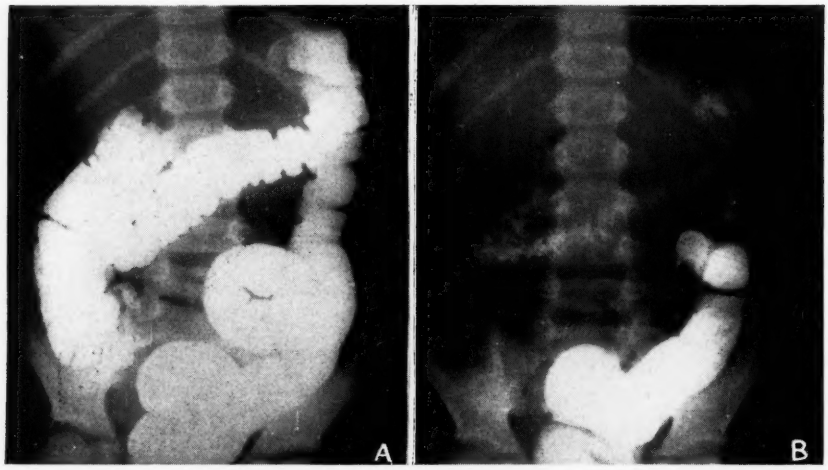

Fig. 5.—Enema studies (P. K.). *A*, Control (barium) enema shows normal filling. *B*, Allergen (egg-barium) enema shows marked spasm of the transverse and descending colon.

constriction of both the transverse and descending colons (Fig. 5), with additional cecal spasm in one. In six, only the transverse colon was constricted; and in one, just the descending colon. Dilatation of the entire colon was seen in one child (Fig. 6). Such changes were almost always accompanied by severe abdominal pain and tenesmus. In six patients no apparent differences between their two studies were visualized; and in these no symptoms were noted despite the large quantities of antigen used.

In the colon, therefore, it seems that constriction is the most frequent finding, dilatation occurring rarely.

Extreme caution had to be exercised because of the danger attendant upon the introduction of an allergen into this highly absorptive organ. As was brought out in a previous communication,[1] a severe constitutional reaction followed the administration of a barium enema containing only one teaspoon of nut.

THE EFFECT OF PROPRIETARY BARIUM MIXTURES

A proprietary barium meal, known to contain milk, malt, and chocolate, was utilized in our earlier studies. These substances soon became

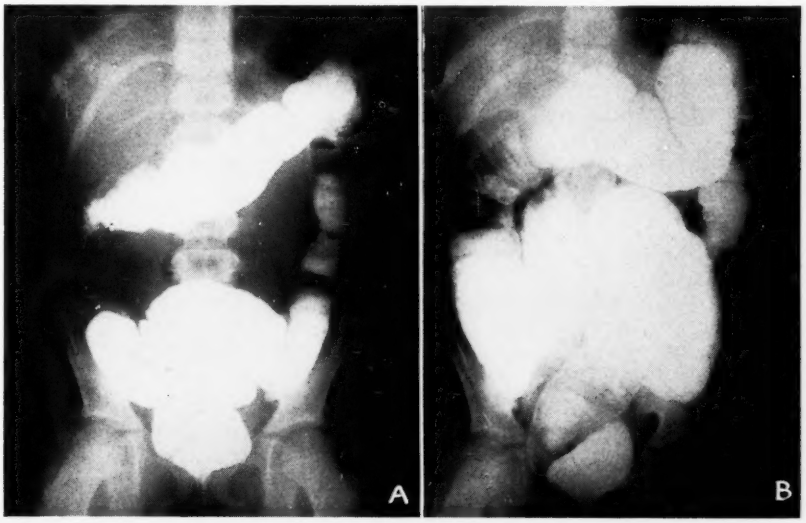

Fig. 6.—Enema studies (A. DeM.). *A*, Control (barium) enema shows normal filling. *B*, Allergen (milk-barium) enema shows generalized dilatation of the entire colon.

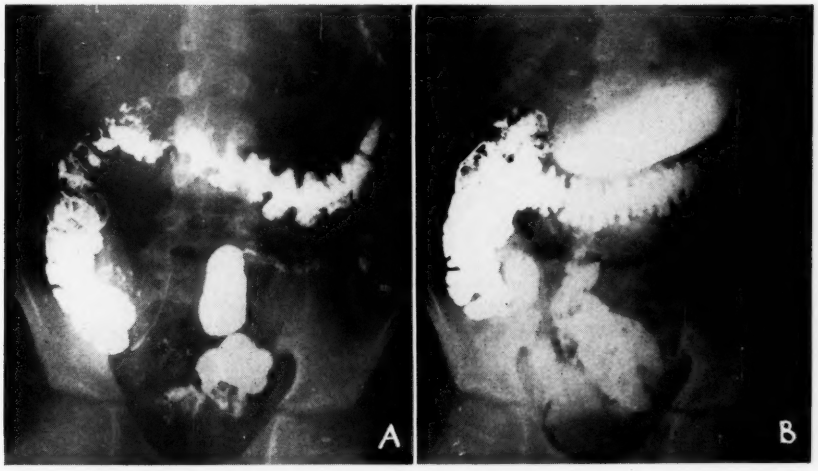

Fig. 7.—Six-hour studies (M. L.). *A*, Plain barium meal reveals no gastric retention. *B*, Proprietary barium meal (consisting of milk, chocolate, malt, and barium) shows moderate gastric retention and spasm of the transverse and cecal portions of the colon.

suspected as possible causes of unexpected variations in the control roentgenograms. It was our impression that this proprietary barium must be antigenic to some degree, since the variations noted in the controls resembled those observed with the allergen-containing meals; namely, gastric retention, colonic spasm, etc. (Figs. 7 and 8), and namely, gastric retention, colonic spasm, etc. (Figs. 7 and 8, and L. S., J. C., and G. T. in Table III). Consequently, in the rest of our studies a control meal consisting of plain barium sulfate suspended in water was used. Our findings confirmed those of Rowe[9] who advised the use of allergen-free mixtures of barium sulfate in the routine examination of individuals with gastrointestinal allergy.

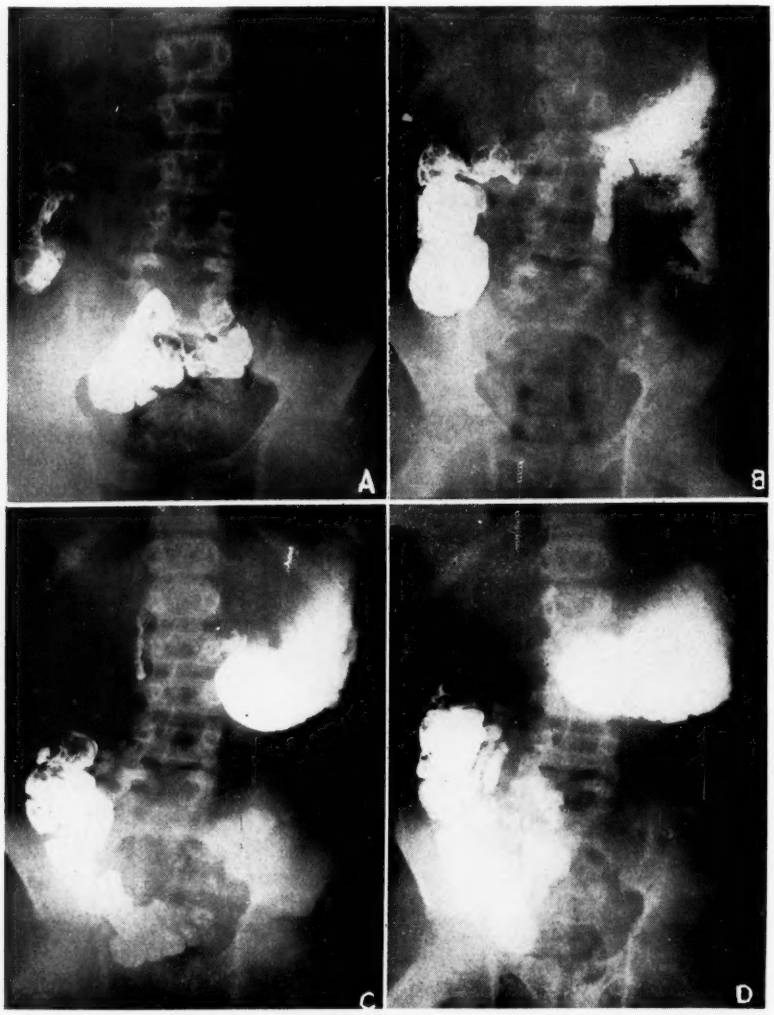

Fig. 8.—A comparison of the antigenic effect of different meals at the six-hour period (I. S.). *A*, Plain barium meal shows no gastric retention. *B*, Proprietary barium meal shows slight gastric retention. *C*, Allergen (egg-barium) meal demonstrates moderate gastric retention. *D*, Allergen (nut-barium) meal demonstrates moderate gastric retention.

An inquiry addressed to several manufacturers of proprietary barium mixtures revealed that the following flavoring materials are commonly incorporated: milk, malt, chocolate, vanilla, acacia, tragacanth, etc. Almost all of these are common allergens.

THE EFFECT OF NONOFFENDING FOODS

It has been pointed out[14-17] that foodstuffs added to barium meals may alter the roentgenogram. To determine whether our abnormal roentgenographic findings were due to this factor and not to any specific sensitiveness, two-thirds of an egg (6 drams) were fed to each of six children who had previously been sensitive to egg but who had apparently lost their sensitivity. This amount was equal to the maximum quantity used in any single feeding during our investigation. To another child, 1 ounce of milk was given. Neither abnormal roentgenograms nor clinical symptoms resulted from the use of these amounts of food. It is noteworthy in this connection that enemas containing the largest amounts of foodstuffs were not necessarily the ones which caused alterations in the roentgenogram (Table IV). Hence the changes which were obtained apparently were due to the allergenic effects of foods and not to their nutritive composition.

REPEATED STUDIES WITH THE SAME OR DIFFERENT ALLERGENS

To determine whether the effect of allergens on the gastrointestinal tract is constant, three children (M. C., R. C., and R. L.) were restudied with the same allergens at a later date. Roentgenographic disturbances similar to those originally observed resulted. One child (I. S.), on three occasions, was fed a different food to which he was sensitive. Delayed gastric emptying and gastric retention at six hours were noted in each trial (Fig. 8).

DISCUSSION

Are any of the findings described above diagnostic of gastrointestinal allergy? Gastric retention was a frequent finding. Increased segmentation of the small intestine and colonic spasm were less common. While these findings are not necessarily pathognomonic, their presence should suggest the possibility of allergic gastrointestinal disturbances, particularly when other allergic manifestations or a family history of allergy is present.

The frequency of the gastric reactions which were demonstrated was probably due to the type of patient selected. These were children known to exhibit immediate gastrointestinal responses. This choice was made because we felt that the causal relationship could not be as definitely established with delayed reactions.

It is our impression that gastric retention on an allergic basis might be caused by some occlusion due to edema of the pyloric mucosa, and,

possibly, by gastric atony (Fig. 1). Inasmuch as pyloric spasm cannot be demonstrated on the roentgenogram, its presence can only be inferred. It is interesting that Walzer[18, 19] has described allergic reactions which were experimentally induced in the gastrointestinal tract of the passively sensitized rhesus monkey, wherein allergic reactions in the animal's stomach were characterized both by extensive edema and by spasm of the pyloric region. Edema of the lower third of the stomach or antrum and diminished peristalsis have been reported by other workers from gastroscopic observations made on the allergic stomach in human beings.[20-22]

SUMMARY

A roentgen study of thirty allergic children with gastrointestinal disturbances due to specific foods revealed the following:

1. Gastric retention was the most common finding. Increased small intestinal segmentation and colonic spasm were also observed, but less frequently.

2. These effects were due to the allergenicity of food and not to its nutritive composition.

3. The inclusion of even small amounts of flavoring foodstuffs in barium mixtures may produce alterations in the roentgenograms of allergic individuals.

We are indebted to Dr. Bernard Epstein and to the Department of Radiology for their kind assistance.

REFERENCES

1. Fries, J. H., and Zizmor, J.: Roentgen Studies of Children With Alimentary Disturbances Due to Food Allergy, Am. J. Dis. Child. **54**: 1239, 1937.
2. Crispin, E. L.: Visceral Crises in Angioneurotic Edema, Collected Papers of the Mayo Clinic, Philadelphia, 1915, W. B. Saunders Co., vol. 7, p. 823.
3. Christian, H. A.: Visceral Disturbances in Patients With Cutaneous Lesions of the Erythema Group, J. A. M. A. **69**: 325, 1917.
4. Duke, W. W.: Food Allergy as a Cause of Abdominal Pain, Arch. Int. Med. **28**: 151, 1921.
5. Andresen, A. F. R.: (a) Gastrointestinal Manifestations of Food Allergy, J. M. Soc. New Jersey **31**: 402, 1934; (b) The Surgeon and Colonic Allergy, Am. J. Surg. **50**: 281, 1940; (c) Gastrointestinal Allergy, South. M. J. **34**: 418, 1941.
6. Gay, L. P.: Radiological Demonstration of an Allergic Reaction in the Mucosa and Musculature of the Colon, Am. J. Digest. Dis. & Nutrition **3**: 181, 1936.
7. Eyermann, C. H.: X-Ray Demonstration of Colonic Reaction in Food Allergy, J. Missouri M. A. **24**: 129, 1927.
8. Serio, F.: La sintomatologia radiologica della anafilassi gastro-intestinale, Riforma med. **48**: 1742, 1932.
9. Rowe, A. H.: Roentgen Studies of Patients With Gastrointestinal Food Allergy, J. A. M. A. **100**: 394, 1933.
10. Hansen, K., and Simonson, M.: Roentgenologic Study of Allergic Gastritis and Allergic Pylorospasm, Röntgenpraxis **9**: 145, 1937.
11. Hampton, S. F.: Henoch's Purpura Based on Food Allergy, J. ALLERGY **12**: 579, 1941.
12. Wing, W. M., and Smith, C. A.: Spontaneous and Induced Sensitivity to Foodstuffs: X-Ray Studies of the Small Intestine in Man and Guinea Pig, J. ALLERGY **14**: 56, 1942.

13. Cooke, R. A.: Protein Derivatives as Factors in Allergy, Ann. Int. Med. **16**: 71, 1942.
14. Prendergass, E. P., et al.: Studies of the Small Intestine: The Effect of Foods and the Various Pathologic States on the Gastric Emptying and the Small Intestinal Pattern, Radiology **26**: 651, 1936.
15. Ravdin, I. S., et al.: Effect of Foodstuffs on the Emptying Time of the Normal and Operated Stomach and the Small Intestinal Pattern, Am. J. Roentgenol. **35**: 306, 1936.
16. Fantus, B., Kopstein, G., and Schmidt, H.: Roentgen Study of Intestinal Motility as Influenced by Bran, J. A. M. A. **114**: 404, 1940.
17. Macy, I. G., et al.: Normal Variation in the Gastrointestinal Responses of Healthy Children, Am. J. Roentgenol. **43**: 394, 1940.
18. Walzer, M.: Allergy of the Abdominal Organs, J. Lab. & Clin. Med. **26**: 1867, 1941.
19. Walzer, M., Gray, I., Strauss, H. W., and Livingston, S.: Studies in Experimental Hypersensitiveness in the Rhesus Monkey. IV. The Allergic Reaction in Passively Locally Sensitized Abdominal Organs, Preliminary Report, J. Immunol. **34**: 91, 1938.
20. Chevallier, R.: L'oedeme fugace de la region antropylorique au cours des gastropathies allergiques. Étude gastroscopique, Bronchoscop., oesophagoscop. et gastroscop. 129-136, 1935.
21. Lundback, K.: Case of Gastroscopically Verified Gastric Edema in Quincke's Disease, Ugesk. f. laeger **101**: 1083, 1939.
22. Pollard, H. M., and Stuart, G. J.: Experimental Reproduction of Gastric Allergy in Human Beings With Controlled Observations on the Mucosa, J. ALLERGY **13**: 467, 1942.

485 OCEAN AVENUE, BROOKLYN, N. Y.
GRANNIS CORNER, NEW HAVEN, CONN.

STATISTICAL STUDIES IN ALLERGY

I. A Correlation Analysis

T. Gaylord Andrews, Ph.D.
New York, N. Y.

IN THE investigations described in this paper and in another one in this series,[1] the main stimulus has been the need for more facts about allergy, and the response has been to use statistical methods in analyzing data in order to find any new facts that may be present. There are, of course, secondary motives involved in this stimulus-response situation. One important secondary stimulus here is my contention that clinicians are not availing themselves of the newer statistical methods for fact finding. Some are even avoiding the older statistical methods as something apart from their training and interests. The study reported here is only the first step in a complex type of statistical analysis; *i.e.*, factorial analysis. The results of this first step, however, appear to be important enough in themselves to warrant their separate consideration.

The field of allergy, being relatively new and being constantly beset with difficulties of diagnosis, therapy, and theory, is gaining ground at a slower pace than had been predicted. Many interesting problems arise in this connection. Most of these problems defy the practicing physician by being so time-consuming, although often some subjective judgments are made. One of these problems is the possibility of determining the relationships between antigen reactions. There is quite an interesting possibility that the typical reactions which patients give to the injection or patch tests in the clinic may group themselves into related clusters or "families." The identification of these patterns of reactions is difficult and unreliable when one uses a simple tallying process or cursorily pools the observations made during clinic rounds. The analysis and possible identification of these patterns of allergic reactions become more interesting when one realizes the possible clinical uses of such a piece of knowledge. Also, such a determination may prove useful in the studies of theory and etiology of allergy. However, although the present study will end with an attempted resolution of the problem of "antigen-reaction families," that end is only coming into view. The present report is on the results obtained from the first step, a correlational analysis.

Reviewing the literature on the problem, one finds few statistically reliable reports on the relationships between responses to one antigen and responses to other antigens. There have been estimates and theories, but beyond these there is much silence.

Department of Psychology, Barnard College, Columbia University.

In the procedure of the present study, the case records of 291 individuals were gathered from the cumulative files of the Allergy Clinic of the Roosevelt Hospital, New York City. The major criterion for the selection process was the completeness of the records. It is doubtful that this criterion for inclusion produced any systematic error of bias in the results. It is assumed that the data collected were fairly representative of the population of allergy patients. The data included, for each patient, the record number (for purposes of rechecking for error), age, sex, type of allergic disorder from which the patient suffered (asthma, urticaria, etc.) and coded degrees of skin reactions to thirty-six test antigens. The skin reaction to each antigen was originally judged by the physicians in charge as either negative, slight, moderate, or marked, thus making an arbitrary four-point linear scale. The antigens used and their corresponding concentrations expressed as protein nitrogen units are listed in Table I.

TABLE I

1. Dust (full strength)	19. Egg white (100)
2. Timothy (100)	20. Milk (casein and whey) (10,000)
3. Rabbit epithelium (100)	21. Wheat (5,000)
4. Feathers (1,000)	22. Beef (5,000)
5. Orris (100)	23. Chicken (5,000)
6. Cottonseed (100)	24. Pork (5,000)
7. Dog epithelium (100)	25. Fish (1,000)
8. Ragweed (100)	26. Shellfish (1,000)
9. Horse epithelium (100)	27. Tomato (5,000)
10. Raw silk (100)	28. Lima bean (5,000)
11. Le Page glue (100)	29. Orange (5,000)
12. Flaxseed (100)	30. Mustard (100)
13. Cat epithelium (100)	31. White potato (5,000)
14. Alternaria (1,000)	32. Rice (5,000)
15. Horse serum (1-100)	33. Green pea (5,000)
16. Pyrethrum (100)	34. Banana (1,000)
17. Aspergillus (1,000)	35. Chocolate (5,000)
18. Kapok (100)	36. Peanut (1,000)

These data were then coded and punched onto hand-sorting cards. The next step was to find the place in each reaction series which was closest to the median (50 per cent point) and to code each reaction of each patient as above or below this crude median. This step dichotomized the graded reactions to each antigen as an arbitrary plus or minus. From this method, the data were easily fractionated into fourfold tables,

TABLE II

		DUST		
		−	+	
TIMOTHY	−	153 (.53)	73 (.25)	226 (.78)
	+	30 (.10)	35 (.12)	65 (.22)
		183 (.63)	108 (.37)	291 (1.00)

TABLE III.

TETRACHORIC INTERCORRELATIONS BETWEEN SKIN

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1.		32	−12	50	19	07	33	29	33	42	37	26	37	16	16	14	10	10
2.	32		40	07	67	66	25	70	45	49	49	61	42	55	17	63	36	63
3.	−12	40		02	43	61	34	32	18	04	32	49	23	34	09	43	49	09
4.	50	07	02		08	−10	27	−05	02	23	21	10	18	−08	−03	20	−07	−04
5.	19	67	43	08		72	30	43	49	56	60	66	47	50	47	68	54	67
6.	07	66	61	−10	72		30	51	40	47	75	59	27	25	57	62	44	75
7.	33	25	34	27	30	30		38	46	40	40	60	69	40	25	30	31	32
8.	29	70	32	−05	43	51	38		07	11	30	35	24	47	20	58	51	54
9.	33	45	18	02	49	40	46	07		53	65	50	42	59	53	48	30	37
10.	42	49	04	23	56	47	40	11	53		69	65	26	32	20	59	33	47
11.	37	49	32	21	60	75	40	30	65	69		68	31	53	44	76	48	57
12.	26	61	49	10	66	59	60	35	50	65	68		42	34	53	67	10	79
13.	37	42	23	18	47	27	69	24	42	26	31	42		33	37	26	55	35
14.	16	55	34	−08	50	25	40	47	59	32	53	34	33		37	52	38	20
15.	16	17	09	−03	47	57	25	20	53	20	44	53	37	37		46	22	40
16.	14	63	43	20	68	62	30	58	48	59	76	67	26	52	46		60	67
17.	10	36	49	−07	54	44	31	51	30	33	48	10	55	38	22	60		56
18.	10	63	09	−04	67	75	32	54	37	47	57	79	35	20	40	67	56	
19.	38	50	49	10	66	59	60	30	70	52	52	70	48	67	45	66	38	64
20.	32	62	25	04	50	46	37	24	53	45	64	58	43	23	62	50	32	52
21.	35	58	22	10	65	67	43	54	40	52	67	78	37	37	30	67	47	72
22.	38	52	42	21	66	50	58	20	63	65	63	63	57	45	47	46	47	36
23.	20	58	42	01	62	50	42	40	55	28	46	43	41	39	47	44	48	32
24.	32	45	53	10	60	63	40	32	60	49	66	62	42	31	47	60	40	48
25.	27	48	56	30	69	60	47	40	40	44	55	43	54	65	36	43	15	28
26.	33	20	17	44	43	30	28	20	−05	43	37	32	27	23	13	51	18	13
27.	26	56	32	22	64	49	39	52	27	31	32	51	46	36	43	58	20	42
28.	00	65	57	04	65	71	31	49	46	38	36	46	24	42	32	57	35	64
29.	00	48	32	09	48	60	20	34	25	39	33	49	16	23	42	48	34	52
30.	08	40	32	10	60	54	47	12	60	63	56	48	38	49	37	43	43	09
31.	23	45	22	20	61	50	24	18	35	40	43	54	46	18	57	51	40	63
32.	47	62	38	35	65	48	35	40	40	53	10	65	36	35	41	64	28	56
33.	25	57	55	08	50	68	12	55	33	17	49	54	37	37	42	50	40	42
34.	06	48	17	04	28	34	03	17	33	28	17	18	−04	12	30	26	32	36
35.	20	43	53	19	60	63	28	30	46	42	53	48	26	31	37	60	12	44
36.	31	70	46	16	80	77	40	42	47	60	48	66	37	30	53	60	50	66

*A decimal point should precede each coefficient. The numbers of the variables correspond to the antigens previously listed.

with each antigen paired with every other antigen in terms of frequency of plus or minus reactions.

As an example of this, the fourfold frequency table for the combination of the first two antigens, dust and timothy, appear in Table II. The unbracketed numbers indicate frequency and the bracketed numbers represent proportion. The immediate interpretation of this table is that 53 per cent of the persons who reacted negatively (lower than the crude group median) to dust also reacted negatively to timothy, 25 per cent of the persons who reacted positively to dust reacted negatively to timothy, etc. Similar tables were set up to show the relationships between all the variables, and from these tables tetrachoric correlation coefficients were derived by using Thurstone's diagrams.[2] These correlations are presented in Table III.

This mass of intercorrelations in Table III represents the type of data that the clinician tends to estimate from experience with large numbers

III.

SKIN REACTIONS TO TEST ANTIGENS*

19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
38	32	35	38	20	32	27	33	26	00	00	08	23	47	25	06	20	31
50	62	58	52	58	45	48	20	56	65	48	40	45	62	57	48	43	70
49	25	22	42	42	53	56	17	32	57	32	32	22	38	55	17	53	46
10	04	10	21	01	10	30	44	22	04	09	10	20	35	08	04	19	16
66	50	65	66	62	60	69	43	64	65	48	60	61	65	50	28	60	80
59	46	67	50	50	63	60	30	49	71	60	54	50	48	68	34	63	77
60	37	43	58	42	40	47	28	39	31	20	47	24	35	12	03	28	40
30	24	54	20	40	32	40	20	52	49	34	12	18	40	55	17	30	42
70	53	40	63	55	60	40	−05	27	46	25	60	35	40	33	33	46	47
52	45	52	65	28	49	44	43	31	38	39	63	40	53	17	28	42	60
52	64	67	63	46	66	55	37	32	36	33	56	43	10	49	17	53	48
70	58	78	63	43	62	43	32	51	46	49	48	54	65	54	18	48	66
48	43	37	57	41	42	54	27	46	24	16	38	46	36	37	−04	26	37
67	23	37	45	39	31	65	23	36	42	23	49	18	35	37	12	31	30
45	62	30	47	47	47	36	13	43	32	42	37	57	41	42	30	37	53
66	50	67	46	44	60	43	51	58	57	48	43	51	64	50	26	60	60
38	32	47	47	48	40	15	18	20	35	34	43	40	28	40	32	12	50
64	52	72	36	32	48	28	13	42	64	52	09	63	56	42	36	44	66
	57	66	78	76	56	68	32	51	60	62	78	54	65	53	48	65	66
57		56	70	70	64	40	10	58	51	49	55	64	49	53	42	51	75
66	56		52	57	61	55	40	69	75	58	56	50	65	76	35	70	80
78	70	52		77	76	72	24	45	62	45	72	55	22	39	37	66	80
76	70	57	77		75	70	19	62	68	50	70	62	60	72	21	73	77
56	64	61	76	75		63	20	60	47	28	52	68	59	52	33	66	72
68	40	55	72	70	63		62	26	60	38	72	52	38	56	32	45	59
32	10	40	24	19	20	62		13	14	24	29	26	39	30	−04	05	40
51	58	69	45	62	60	26	13		57	75	49	59	63	76	−13	−16	00
60	51	75	62	68	47	60	14	57		72	73	55	63	86	47	60	76
62	49	58	45	50	28	38	24	75	72		50	55	44	75	41	49	61
78	55	56	72	70	52	72	29	49	73	50		53	53	55	56	62	79
54	64	50	55	62	68	52	26	59	55	55	53		78	57	38	50	60
65	49	65	22	60	59	38	39	63	63	44	53	78		70	20	70	70
53	53	76	39	72	52	56	30	76	86	75	55	57	70		40	52	70
48	42	35	37	21	33	32	−04	−13	47	41	56	38	20	40		32	68
65	51	70	66	73	66	45	05	−16	60	49	62	50	70	52	32		93
66	75	80	80	77	72	59	40	00	76	61	79	60	70	70	68	93	

of patients. However, it is quite apparent that the clinician will not be able to hold a matrix of this size and complexity in memory for any length of time. Also the clinical estimates are not as accurately computed or expressed as are these data. This type of data offers some very interesting problems for analysis. Primarily, a coefficient of correlation is a mathematical expression of the relationship between variables. The variables in this case are the graded degrees of reaction to the antigens. Tetrachoric correlations are a type of correlation estimate from a fourfold frequency chart in which one may assume that the variables, if linearly measured, would present a symmetrical and normal distribution. In the data employed in this study such an assumption may or may not be completely warranted. It may be supposed that if smaller gradations in the reactions of the patients could have been measured and distributed, a normal distribution would result for most of the variables here. However, such an hypothesis could not be tested. At any rate, the tetrachoric correlation coefficient forms an estimate of the prob-

able linear correlation that would be obtained if the data were distributed linearly.

The data in Table III are arranged in a logical fashion. Each column and each row corresponds to the number of the antigen noted. As an example of how the table is to be used, one may read down the first column and note the correlations. Column 1 represents dust antigen. First, we note a correlation of .32 between dust and timothy (the second antigen in listed order), further down the column to number 10 we find dust correlates with raw silk .42, etc. It will be noted that one may go horizontally through the table in the same manner, the numbers being listed in both directions. The first thing that is apparent in this intercorrelation table is that most of the coefficients are positive. The few minor exceptions to this are so low as to be unreliable.* This indicates that, as far as these antigens employed and the patients tested are representative, there are no real inverse relationships in reactions to antigens. If there is any tendency at all, sensitivities tend to go together. Knowing a marked reaction to one antigen does not enable us to estimate a probable lack of reaction to some other particular antigen. Although this fact is probably generally assumed by now in the field of allergy, it is nevertheless interesting information from the present data.

Another observation from the table is the wide variation in the degrees of relationship represented. The correlation coefficients range from .00 to .93. This variability in itself offers some important information. In the first place, some sensitivities tend to go together very closely, while some others are apparently not related at all. Although it is the subject matter of the next paper to be presented on this topic, an important question arises as to what these highly related sensitivities have in common. This point will be left for later reference. It is to be inferred that the clinician, by knowing some of a patient's sensitivities, can make some predictions about his other sensitivities. The reliability of such predictions is proportional to the size of the correlations involved. There is no antigen reaction represented that does not correlate significantly (above .22) with some other antigen reaction.

A great many of the correlations are of extreme size. It is seldom that one finds correlations of these degrees in such seemingly heterogeneous material, and this point is an extremely interesting one. As an example of some of the interpretations possible, we may take the correlation of .93 between reactions to chocolate (antigen No. 35) and to peanut (antigen No. 36). Squaring this number, one obtains .86, which is the coefficient of determination.[3] This represents the fraction of the variations in reactions to peanut that is attributable to or associated with the factors involved in the reactions to chocolate. Now 86 per cent association is very high, leaving only 14 per cent to represent the nonassociated factors. Of course, it is not readily seen that these factors

*In order to be judged as being significant statistically, a tetrachoric correlation coefficient, with 291 cases, must be greater than plus or minus .22

are biochemical or physiologic in nature. This test was performed on the highest correlation in the matrix. Inspection of the squares of the smaller correlation coefficients shows many slight and insignificant (for prediction) degrees of association. It is to be noted that this method of finding extent of association does not give any information about the character of the association. The index of forecasting efficiency is another device which gives an estimate of the degree of efficiency of predictions from a correlation coefficient.*[4] This is obtained by subtracting from 1 the square root of the expression 1 minus the correlation squared. In the example of the correlation of .93 between reactions to peanut and chocolate, the coefficient of forecasting efficiency would be .63; that is, about 63 per cent efficiency would be involved in predictions from one variable to the other. Naturally this statistic decreases rapidly as the size of a correlation coefficient decreases. Using this test on one of the lower correlations, .50 between dust (antigen 1) and feathers (antigen 4), we find the coefficient of forecasting efficiency (sometimes called the coefficient of dependability) to be only .13. Thus the efficiency of prediction between these two variables would be 13 per cent. Something is to be noted here which may alter the exact interpretations of the above measures, and that is the fact that these derived methods of evaluating correlations are based on product-moment correlations and are not strictly for use with tetrachoric correlations. Usage of tetrachoric correlations merely serves to decrease the reliability of the correlation expression somewhat and so make for comparable changes in the correlation tests described. It may seem, on the basis of the above tests, that the correlation coefficients presented in this study do not tell much after all. However, it would be an interesting challenge to match the efficiency of predictions made so far by clinicians with the calculated efficiency of predictions based on the data presented here.

It is readily acknowledged that these data raise many more questions than they answer. As examples, we may go through the table and pick out some correlations at random. Why is there such a high relationship between peanut (antigen 36) and chocolate (antigen 35), that is .93, and a zero relationship between peanut and tomato (antigen 27)? Is it due to the greater similarity in the chemical components (oils) in chocolate and peanuts, or does it involve a greater similarity in the physiologic processes involved in the assimilation of the two? What do fish (antigen 25) and lima beans (antigen 28) have in common, correlation .60, that shellfish (antigen 26) and lima beans do not, correlation .14? It becomes more complex when we compare contact antigens and food antigens. Why is there a tendency, correlation .60, for people who react to horse epithelium (antigen 9) also to react to pork (antigen 24)

*In employing the coefficient of determination and index of forecasting efficiency, it is to be understood that these devices serve merely as estimates (unbiased) of constants that would hold for the universe of allergy patients. These are "best estimates," but one must realize that a coefficient of determination of 0.86 means merely an approximate value.

but not to shellfish, correlation –.05? It is interesting to see the comparison between the correlations with beef (antigen 22) and the correlations with pork (antigen 24). Although they are not the same thing and correlate .76 with one another, they form a pattern throughout the matrix. Where one correlates highly with another antigen, the other tends to also; where one correlates low with another antigen, the other does also. The more one studies these correlations, the more amazing some of the relations become. A check in some cases is immediately offered to the clinicians who have noticed similarities in reactions to different antigens when testing large numbers of patients. Some such clusters of correlations as horse-dog-cat and kapok-cottonseed are found in these data which corroborate the clinical findings.

There are many other questions which arise from these data, and clinicians may find several different uses for them. That, however, is not the immediate problem which this study was devised to answer. The writer is more interested in the light that these correlations may throw on causes. A most pertinent point involved in this analysis is the significance of "families" or patterns of reactions (sensitivities). In many cases the correlations appear to fall into different clusters, and the significance of these clusters, both diagnostically and theoretically, is an important problem. The next paper in this series[1] will be devoted to a factor analysis of the independent groups of sensitivities represented in this matrix of intercorrelations, and an attempt will be made to interpret the separate factors.

The author wishes to express his gratitude to Dr. R. A. Cooke for his cooperation in making the data for these studies available.

REFERENCES

1. Andrews, T. Gaylord: Statistical Studies in Allergy. II. A Factorial Analysis. In preparation.
2. Thurstone, L. L., et al.: Computing Diagrams for the Tetrachoric Correlation Coefficient, Chicago, 1933, University of Chicago Press.
3. Ezekiel, M.: Methods of Correlation Analysis, ed. 2, New York, City, 1941, John Wiley & Sons, p. 139.
4. Garrett, H. E.: Statistics in Psychology and Education, New York City, 1940, Longmans, Green & Co., p. 345f.

SENSITIVITY TO AILANTHUS POLLEN

With Report of Two Clinically Sensitive Patients

George I. Blumstein, M.D.
Philadelphia, Pa.

IN A previous communication[1] it was reported that the unusual tree pollens not routinely used in skin testing were of no etiologic significance in precipitating hay fever in or around the Philadelphia district. Since that time, Rowe[2] has reported a case of pine pollen allergy, Swineford[3] has published a case of hay fever due to the catalpa pollen, and Derbes[4] has cited four patients who were clinically sensitive to the pollen of the linden tree. Clinical sensitivity of two patients to Ailanthus pollen prompted this publication. It also permits a modification of the original conclusion so as to include this and other tree pollens that might, from time to time, prove to be of etiologic significance in precipitating allergic symptoms.

The tree of heaven[5] (*Ailanthus glandulosa*), also known as the Paradise Tree, Ailanthus, Haven-wood and Chinese Sumach, is native to China but has been widely planted in Ontario, Canada, and northeastern United States. A Jesuit missionary brought it into Europe in 1751,[6] hoping that it might establish the silk industry on the continent. A Long Island nurseryman introduced this tree to the United States in 1820.[7] The tree grows rapidly, is not attacked by insects, and tolerates almost any kind of soil and dense shade. The rapid and free growth of the root sprouts makes it almost impossible to eradicate when once established. Only the fertile plant should be used for street planting, as the males exhale a disagreeable odor when flowering and the pollen is said to cause catarrhal trouble.[8] It is naturalized extensively in the eastern, southern, central, and western parts of Pennsylvania, being rare or entirely absent in the northern part.

The tree of heaven can be distinguished in the winter by its stout twigs which are covered with fine down and conspicuous scattered lenticels, and contain a large, light brown pith. The twigs are roughened by large heart-shaped leaf scars, containing a curved line of bundle scars. In the summer the large alternate leaves, with eleven to fourteen leaflets, which often have glands on the lower surface, are distinctive. The bark cannot be confused with that of any native tree. Flowers appear about June when the leaves are fully developed. Pollination begins in early June and lasts a little over three weeks.

Commercially the tree is relatively unproductive. The wood takes a high polish and may also be used for woodenware and for making charcoal.[9] The leaves are frequently mixed with sumac leaves, the latter con-

From the Allergy Clinic of Mount Sinai Hospital, Philadelphia, and from the Clinic of Allergy and Applied Immunology, Temple University Hospital and Medical School.

taining 20 to 35 per cent tannin, and may be utilized in the tanning industry, more especially for the pale colors and soft tanning as for moroccos, roans, and skivers.[10] Two species, *A. sutchuenensis* and *A. vilmoriniana* are sometimes planted as the host of a silkworm (*Attacus cynthia*) producing a coarse silk, inferior to that of the common silkworm.[8]

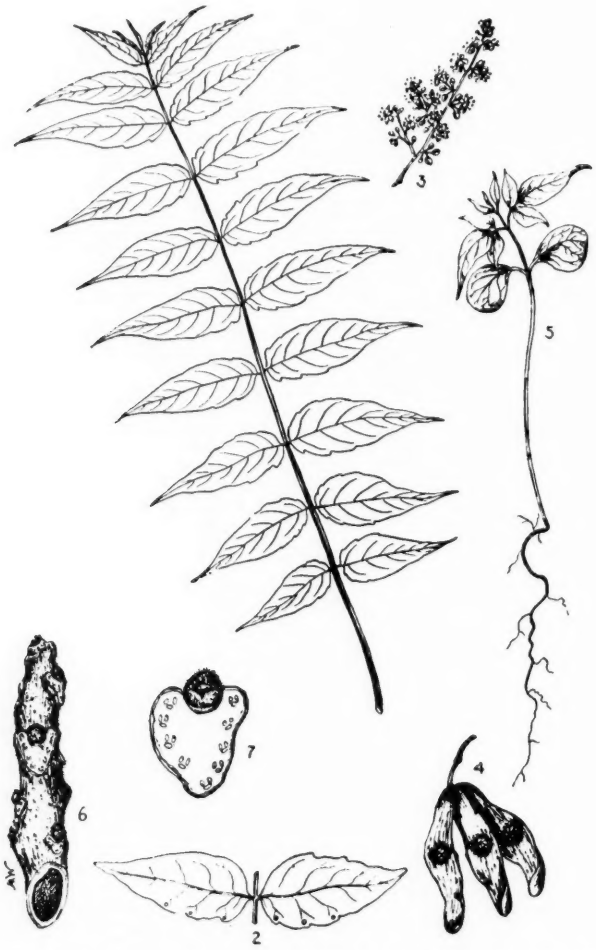

Fig. 1.—Tree of heaven. *1*, A mature leaf (×½); *2*, lower side of two leaflets showing glands (×½); *3*, a panicle of flowers (×½); *4*, a small cluster of winged seeds (×½); *5*, a seedling (×½); *6*, a winter twig (×½); *7*, a bud and a leaf scar with bundle scars (natural size).

CASE REPORTS

CASE 1.—S. S., male, aged 51, fruit merchant by occupation, was first seen on May 13, 1936, because of spring and fall hay fever and asthma of seven years' duration. The spring symptoms began in early June and invariably subsided before July 4, while the fall symptoms began in mid-August and continued until late September or until the first frost.

One of the outstanding objective signs of his spring hay fever was the marked conjunctival reaction. The conjunctivitis was one of the earliest signs of hay fever and persisted throughout the period of symptomatology. Bronchial asthma appeared at the height of pollination and persisted for several weeks. He had obtained relief from his fall symptoms by visits to Bethlehem, N. H., Phoenix, Arizona, and San Francisco. A polypectomy was performed in 1933. One brother and one sister were afflicted with ragweed hay fever and asthma.

Skin tests revealed marked reaction to ragweed pollen, slight reactions to timothy and plantain pollen, and negative skin reactions to the usual hay fever causing tree pollens in this locality. Ophthalmic and nasal tests were done with all the grass and tree pollens known to cause clinical hay fever in this area, but negative reactions resulted. This eliminated these pollens[11] as etiologic factors and suggested either an unusual pollen or mold as the probable offending agent. Skin and nasal tests with all the mold extracts available proved negative, thus suggesting that his symptoms were due to an unusual pollen.

Phylactic treatment with extracts of timothy and plantain pollen during the 1936 season failed to afford any relief whatsoever. Symptoms began on May 29 and subsided on June 24. During the following season he was treated with oak and sycamore pollen extracts in addition to timothy and plantain, since these trees pollinated at or about the time that clinical symptoms appeared. Symptoms of similar severity and duration made their appearance on May 26, 1937, and subsided on June 23, 1937. In 1938 treatment with timothy and plantain pollen extracts again failed to afford relief, symptoms appearing on June 4 and lasting until July 2. In 1939 symptoms began on May 31 and lasted until June 25. It was at that time that I realized that a distinct correlation existed between the patient's symptoms and the blooming of an Ailanthus tree in the rear yard of his home. Careful questioning verified this suspicion, and an extract of Ailanthus containing 0.1 mg. of nitrogen per cubic centimeter was prepared. Intradermal testing with this latter extract evoked a markedly positive skin reaction. Eye and nasal tests with the dry pollen were also positive. A change of residence during the fall of 1939 raised hopes that the new location might be free from this tree, but a complete survey of the tree flora revealed many Ailanthus trees within a short distance of his home. Treatment with an extract of Ailanthus pollen was considered satisfactory during the 1940 season, since the patient had only mild hay fever symptoms from June 19 to June 23 and no annoying asthmatic seizures. During this entire time results of treatment of his fall hay fever with a ragweed pollen extract were considered satisfactory. The patient moved to Los Angeles in the winter of 1940 and has been free from spring symptoms since. A superficial survey by the patient failed to reveal the existence of the Ailanthus tree in his locality.

CASE 2.—E. B., female, stenographer, aged 27, consulted me on Feb. 15, 1940, because of "rose fever" that had occurred each year from late May until mid-July for the past six years. The symptoms were always worse during the first three weeks of June. There was very little sneezing and only a mild rhinorrhea, but the ocular symptoms were severe and annoying, consisting of itching, tearing, photophobia, and conjunctival injection. She was symptom free while on an ocean voyage during the 1939 season. Her sister suffered from ragweed hay fever.

Skin tests to all the pollens found in the air at or about that time of the year were negative. Ragweed pollen, however, gave a markedly positive reaction. All the ophthalmic and nasal tests, including ragweed, were negative. An accurate etiologic diagnosis could not be made, and the patient was asked to return during the period of active symptomatology. She reported on June 15, 1940, when symptoms first appeared. It was at that time that careful questioning revealed the existence of an Ailanthus tree in her immediate environment. It also recalled to her mind the fact that her symptoms were always associated with the blooming period of this tree. By June 30 all the symptoms of hay fever had subsided. Skin, eye and nasal tests were positive to Ailanthus pollen, and the patient was treated with an Ailanthus pollen extract during 1941. Mild but unannoying symptoms of hay fever were present from May 31 to June 15. The patient manifested a dry, nocturnal cough during the height of pollination. On March 28, 1942, a dose of 0.1 c.c. of the concentrated 3 per cent Ailanthus pollen extract resulted in a constitutional reaction manifested as severe, lower abdominal cramps that prevented her from straightening up. The administration of 0.5 c.c. of 1:1000 epinephrine solution afforded her relief within fifteen minutes. Distinct bronchial asthma occurred during the height of pollination in 1942, but the oculonasal symptoms of hay fever were mild as compared with previous years when the patient had not received treatment.

The constitutional reaction occurred with a change from an old to a new pollen extract. The pollen used in the preparation of this latter extract was obtained from a new source. In the interim another extract of Ailanthus pollen had been found incapable of evoking either positive skin or mucous membrane reactions. Skin tests and passive transfers showed that the three pollen extracts used varied widely in their antigenic activity. All three extracts (3 per cent) were prepared in the same manner but no nitrogen determinations were performed.

DISCUSSION

The nonmedical literature as far back as 1900[12] contains a statement that the Ailanthus pollen is said to cause catarrhal trouble, yet no medical reference alludes to or corroborates this statement. Alfred Rehder,[13] in a personal communication regarding the origin of it, said

that there must be some published reference before 1900 regarding the effect of the pollen. Careful search for such an article, however, has been fruitless. Nonetheless one must assume that the author responsible for the statement must have known of a patient who suffered during the time that the Ailanthus tree was pollinating.

This report of two patients exhibiting clinical sensitivity to Ailanthus pollen together with the reports of Rowe, Swineford, and Derbes regarding pine, catalpa, and linden sensitivity should emphasize the potentialities that these and other pollens possess and the role that they might play in precipitating clinical allergy. Because of the rarity of such cases, routine testing with the uncommon tree pollens is inadvisable. They should, however, be thought of and tested for in the obscure cases. The local flora of unusual trees and plants, plus the knowledge of their approximate period of pollination, should be the determining factors in deciding which pollens to use in skin testing.

Clinically, there is nothing characteristic about sensitivity to the pollen of the Ailanthus tree. There was, however, one outstanding feature in the cases cited that might aid in the clinical diagnosis. This was the marked conjunctivitis that persisted throughout the pollinating season and subjectively was the most annoying symptom.

Pollen obtained from different sources varied widely in antigenic activity. This should serve to stress the necessity for testing the activity of each new extract. Had this been done, the constitutional reaction encountered could have been avoided.

The experience in these cases emphasizes the fact that positive skin reactions, per se, are not indicative of clinical sensitivity, as indicated by the positive reactions to timothy and plantain in Case 1. They must be correlated with the clinical history, period of pollination, and observation during the season before they assume significance. The nasal test with the powdered material is a simple office procedure that enables the examining physician to evaluate the significance of a positive skin reaction in cases of pollen allergy, as exemplified in these two case reports.

SUMMARY

1. Cases of two patients clinically sensitive to Ailanthus tree pollen are presented. The marked conjunctivitis was a noteworthy clinical feature in the cases cited.

2. The variability of antigenic activity of pollen obtained from different sources is discussed.

3. The value of the nasal test in cases of pollen allergy is again stressed.

REFERENCES

1. Tuft, L., and Blumstein, G.: Incidence and Importance of Tree Pollen Hay Fever With Particular Reference to Philadelphia and Vicinity, J. ALLERGY 8: 464, 1937.

2. Rowe, A. H.: Pine Pollen Allergy, J. ALLERGY **10**: 377, 1939.
3. Swineford, O.: Catalpa As a Cause of Hay Fever, J. ALLERGY **11**: 398, 1940.
4. Derbes, V. J.: The Linden As a Factor in Seasonal Pollinosis, J. ALLERGY **12**: 502, 1941.
5. Illich, J. S.: Pennsylvania Trees, Bull. 11, Pennsylvania Department of Forests and Waters, 1925.
6. Green, C. H.: Trees of the South, Chapel Hill, 1939, University of North Carolina Press, p. 320.
7. Rogers, J. E.: Nature Library, Vol. 11, Trees, Garden City, N. Y., 1907, Doubleday, Page & Co., p. 351.
8. Rehder, A.: Standard Cyclopedia of Horticulture by L. B. Bailey, New York, 1914, The Macmillan Co., vol. 1, p. 241.
9. Hottes, A. C.: The Book of Trees, New York, 1932, A. T. De Le Mare Co., Inc., p. 176.
10. Bailey, L. B.: Cyclopedia of American Agriculture, New York, 1911, The Macmillan Co., vol. 2, p. 626.
11. Blumstein, G. I.: Dry Pollen Nasal Test, J. ALLERGY **8**: 321, 1937.
12. Bailey, L. B.: Cyclopedia of American Agriculture, New York, 1900, The Macmillan Co., vol. 1, p. 38.
13. Personal communication With Alfred Rehder.

319 S. 15TH STREET

ALLERGY TO FOOD ODORS

Its Relation to the Management of Infantile Eczema

Arthur J. Horesh, M.D., Cleveland, Ohio

IN RECENT years many articles have been written that emphasize factors, other than foods, which contribute to the etiology of infantile eczema (atopic dermatitis). While elimination of foods from the diet controls some cases, it is generally recognized that this procedure often fails to bring about satisfactory results in a large number of patients afflicted with this troublesome condition. That inhalants are an important factor in obstinate cases is a fact now generally accepted, and it has been shown that removal of environmental substances, in addition to elimination of certain foods, offers greater possibility of success than dietary control alone. These environmental substances include house dust, feathers, wool, silk, pollens, and in general that group of allergens known as inhalants.

That foods may act as inhalants and produce allergic symptoms has been reported, but in my opinion, insufficient importance has been assigned to this factor in the management of infantile eczema.

When foods to which an infant is sensitive are discovered, it is generally believed that the removal of these foods from the diet is all that is necessary to control the allergic symptoms from these foods. This is probably true in the majority of cases, but the mere presence of the foods in the immediate environment of some infants can produce allergic symptoms of a serious degree. It is the purpose of this article to report a few of these cases.

CASE REPORTS

Case 1.—In M. B., a male infant, 13 months old, eczema had developed at the age of 2 months. During the following eleven months he had become progressively worse. Itching was intense. Examination revealed a generalized dry, scaly type of atopic dermatitis. Skin tests for ninety different substances, including the common foods and dusts, revealed the following positive reactions: egg +++, beef ++, chicken ++++, pork ++, wheat ++, rye ++, barley +, fish ++, spinach ++, string bean ++, cabbage ++, cauliflower ++, tomato ++, apple ++, banana +++, house dust ++, feathers +. The patient's response to elimination procedures and to hyposensitization to dust was excellent and after two months of therapy his skin had nearly reached a normal state, except for occasional flare-ups. The mother insisted that these flare-ups occurred whenever a chicken was brought home from the market. She reported that symptoms occurred within two minutes after the package of freshly dressed

From the Babies and Childrens Hospital, and the Department of Pediatrics, School of Medicine, Western Reserve University.

chicken was opened in the child's presence. Sensing that I was not fully convinced of this, she gave me the opportunity of actually witnessing the reaction. I visited the home and became convinced that the mother was correct. The infant's skin was in excellent condition at the time this demonstration took place. When the fully dressed fowl was brought into the presence of the child, within a few minutes he became extremely irritable and began to scratch violently. His skin became warm and flushed, and blotchy red spots and a few wheals appeared on his face, back and abdomen. Within two hours definite exacerbation of his eczematous lesions occurred.

Case 2.—M. J. C., aged 12 years, had had eczema since birth. This case is interesting in that the patient was old enough to describe her own sensations. Examination revealed severe atopic dermatitis over the entire body, with extensive lichenification. Allergic tests for over 150 different substances revealed the following cutaneous sensitivities: egg +++, wheat ++, milk ++, tomato +, pineapple ++, house dust ++, feathers ++, wool ++, orris root +, goat dander ++, rabbit dander ++, jute ++, cat dander ++. Dietary elimination procedures and hyposensitization to environmental allergens brought about remarkable improvement. After one year of treatment her skin was practically normal except for some lichenification. There were, however, some occasional minor flare-ups which were usually attributed to some dietary indiscretion. This patient was extremely sensitive to egg, and her diet was therefore absolutely egg free. About this time and after her skin had been in excellent condition for several months, she had a sudden major flare-up of her eczema. She had been in cooking school and when eggs were being opened she suddenly experienced such intense itching that she was compelled to leave the room. She came to see me the next day because of severe exacerbation of the eczematous lesions. This same reaction, although it was less severe, occurred several times subsequently in her own home. A follow-up examination and test two years later showed that the patient's skin was entirely free from eczema but that egg was still an offending substance. She continued to avoid egg in her diet. When an egg is broken in her presence the patient reports: "I become itchy all over, but if I go out of the room and apply some ointment, I do not break out."

The foregoing stories are typical. The following brief summaries give the pertinent data in seven other cases.

Case 3.—B. M., a male infant, 11 months old, had had eczema since the age of 4 months. Allergic reactions were as follows: egg ++, milk ++, apple +, cod fish ++, salmon ++, halibut ++, pike ++, perch ++, pea ++, beans ++. Exacerbation of the eczema occurred every time fish was fried.

Case 4.—J. D., a female infant, 7½ months old, had had eczema since the age of 4 months. Allergic reactions were egg +++, cow's milk

+, tomato ++, spinach +, carrots +, rice ++, rye +, wheat +++. On two occasions the skin broke out when eggs were opened in the infant's presence.

CASE 5.—J. W., a male infant, 7 months old had had eczema since the age of 2 months. Allergic reactions were egg ++, beef ++++, pork ++, cow's milk +, wheat ++, oats ++, rye ++, barley ++, potato ++, pineapple +++, orange ++. His skin broke out badly after pork was fried in his presence.

CASE 6.—P. M., a female infant, 8 months old, had had eczema since the age of 3 months. Allergic reactions were egg ++++, cow's milk ++, wheat ++, oats ++, barley +, beef ++, potato ++ tomato +, squash ++, apple +, banana ++, apricot +, orange ++. There was exacerbation of the eczema on several occasions when eggs were opened in her presence.

CASE 7.—J. E., a female infant, 10 months old, had had eczema since the age of 4 months. Allergic reactions were egg +++, cow's milk +, beef +, pork ++, lamb ++++, wheat ++, rice, +, rye +, orange +, apple ++, banana +, potato +, peas +++, string bean +, asparagus ++, tomato ++, house dust ++, wool ++. Her skin broke out severely after bacon was fried when she was present.

CASE 8.—M. B., a male infant, 20 months old, had had eczema since the age of 1 year. Allergic reactions were cow's milk +, beef ++, pork ++, wheat ++, rye ++, cabbage, ++, turnip +++, cauliflower ++, mustard ++, peas ++, beans ++. His skin broke out and itched severely after cabbage was cooked in his presence.

CASE 9.—M. F., a male infant, 13 months old, had had eczema since he was 5 months of age. Allergic reactions were egg +++, cow's milk +++, wheat ++, oats ++, rice ++, rye ++, barley ++, banana ++, string bean ++, cabbage family +++. Definite exacerbation of eczema was noted whenever eggs were opened in his presence.

COMMENT

The nine cases described above were collected over a period of seven years in a university allergy clinic and in private practice. The number of cases is small because only those patients were selected which satisfied conditions suitable to well-controlled observations. I am certain that sensitivity to food odors in eczema occurs more frequently than this report indicates. But observations in most patients with eczema, who usually are exquisitively sensitive to a large number of antigens, are difficult to control. The small number of cases reported, therefore, is no index of the frequency of this condition. It is an index of the difficulty of observing cases under the controlled conditions suitable for a convincing report. In all the above cases the patients had made remarkable improvement and were doing well except for sudden acute

flare-ups. Thus in all nine cases the reaction to food vapors was noted only after the eczematous condition was under control by previous elimination or desensitizing procedure. Exacerbations occurred on exposure to the offending vapors. In every case the scratch skin test to the offending substance was definitely positive from two to four plus. In every case the patient's skin remained clear when proper precautions were taken.

That many foods, as inhalants, can produce allergic symptoms is a fact that has long been accepted by allergists. It has been applied chiefly to foods in the raw state which form dusts, such as wheat flour, rye flour, and soy bean meal. Some observers[1, 2] have noted symptoms from the frying of foods. Zohn[3] reported sensitivity to spinach by inhalation. Feinberg and Aries[2] reported cases in which the cooking of shrimp, peas, beans, and lentils provoked attacks of asthma. I have observed[4] an obstinate case of asthma in a child, the cause of which was finally traced to the mere presence of white potato in the environment. The fact remains, however, that scant attention is paid to the importance of food odors or vapors in the control of allergic conditions. Many foods which heretofore have been considered to exert their influence only when they are ingested, can also cause symptoms merely by their presence in the patient's environment. Egg is frequently an offender in this way in patients with infantile eczema. Many of these infants will become definitely worse within a few minutes after exposure to egg.

The management of infantile eczema has always been a difficult problem. Many physicians prefer to rely on local measures only. Those who have approached these patients from the allergic standpoint have often been at a loss to explain the poor results obtained when infants have been placed in a relatively allergen-free environment and have subsisted on only one or two foods. Some observers believe that factors other than sensitivity to allergens are concerned. It is my belief that sensitivity to allergens explains all these cases and that failure occurs in patients who have extreme multiple sensitivity and whose antigens have not been recognized or have been only incompletely removed.

Not all patients suffering from eczema are troubled by foods odors or vapors. It would appear that many allergic infants have sufficient tolerance so that dietary elimination alone suffices to control the symptoms. To compel parents to remove foods completely from the environment in every case would entail endless hardship in a family which already is greatly strained by the many difficulties in the path of controlling an allergic condition. It must be stressed, however, that the factor of inhalants should be considered in allergic patients who are difficult to control. Time and again infants with eczema who appear to have been doing well will suddenly become definitely worse for reasons which it is not possible to explain. Sometimes this is due to acquisition of some new sensitivity. Many times, however, I have found that some food, acting as an inhalant, is the cause of these exacerbations. To keep

the infant out of the kitchen when foods are being prepared is usually sufficient to control the symptoms.

The inhalant factor in food allergy has not yet been thoroughly investigated. Experiments using the Prausnitz-Küstner technique have been performed on the effect of ingestion of foods, but to my knowledge no experiments have been done on the effect of the inhalation of the vapors and odors from foods. It is probable that this factor is important only in cases of extreme sensitivity. Since extreme sensitivity is so common in infantile eczema, however, symptoms produced by food odors are not of rare occurrence. Only when the possibility of an inhalant factor is kept in mind by both the parents and the physician do they appreciate how frequently symptoms are elicited by this route.

The case reports given indicate that, in infants who are sensitive to certain foods, allergic symptoms can be provoked by the inhalation of vapors or odors from that food. Whether infants can be sensitized by this route is not known. Most infants with eczema are sensitive to egg, even though this food has never been a part of their diet. It is generally believed that this sensitivity develops in utero by placental transmission of antigens, or from the passage of antigens in breast milk in nursing infants. Whether the amount of antigen taken in by inhalation of food odors or vapors is sufficient to produce sensitivity is a question that must be answered by the results of further study.

SUMMARY

1. A series of nine cases of atopic dermatitis is reported. In these patients allergic symptoms were provoked by inhalation of vapors or odors from foods, either cooked or raw.

2. The importance of recognizing this factor in the management of infantile eczema is stressed.

3. The possibility of sensitizing infants to foods by this route is considered.

REFERENCES

1. Coca, A. F.: Asthma and Hay Fever, Springfield, Ill., 1931, Charles C Thomas, p. 428.
2. Feinberg, S. M., and Aries, P. L.: Asthma From Food Odors, J. A. M. A. **98**: 2280, 1932.
3. Zohn, B.: An Unusual Case of Spinach Hypersensitiveness, J. Allergy **8**: 381, 1937.
4. Horesh, A. J.: Allergy to Odor of White Potato (Irish Potato), J. Allergy. In press.

Special Report

ALLERGIC RHINITIS DUE TO SPANISH MOSS

GEORGE ADGATE DEAN, M.D.
FAIRPORT, N. Y.

SPANISH moss (*Tillandsia usneoides*) is widespread as a native plant in Florida and some of the other southern states. It bears a small inconspicuous flower, whose pollen does not seem to be a factor in the production of hay fever. Metzger[1] investigated the possibility of sensitivity to the pollen and to the ground fiber of the plant on fifty patients without finding evidence of sensitivity to either.

The fiber of Spanish moss has long been used in packing, especially for shipping fruit. More recently it has been found to be a good upholstery stuffing and is being used more and more for that purpose. The fiber used for stuffing is a black, brown, or tan thread from two to eight inches long and is loosely curled. At about two-inch intervals, there are enlargements of the fiber giving a knotty appearance. This fiber does not mat with age as kapok does.

A search of the literature fails to reveal a report of sensitivity to Spanish moss, so that I believe the following case to be the first reported.

F. E., white male, 31 years of age, machinist. This patient's history, from the allergic standpoint, was negative until 1935 when he moved from Rochester, N. Y., to Fairport, N. Y. At this time he developed a stuffy, copiously running nose which began to discharge every night after supper without regard to the season of the year. On Aug. 14, 1937, he began to have typical ragweed hay fever which disappeared with frost. In 1938 he consulted a physician and received treatment with house dust and ragweed extracts by injection. The results were good as far as the seasonal symptoms were concerned. His perennial rhinitis continued, however, and gradually became worse. He continued his preseasonal ragweed treatment until 1940, when he had severe hay fever and some slight asthma which lasted until Christmas. In 1941 he had good results from the ragweed injections but continued to have his perennial rhinitis nearly every night throughout the year. Skin tests at that time were 4 plus to dust, ragweed, and pyrethrum. Questionable tests occurred to cattle dander, tomato, pea, and wheat. Physical examination showed a boggy, wet nasal mucous membrane. The lungs were clear and otherwise the physical examination was negative.

Upon closer questioning, it was discovered that the patient's perennial rhinitis began as soon as he moved to his present house where he first had his own furniture and that his symptoms always occurred to a marked degree when he was in his living room. He became symptom free when in other rooms in the same house. In 1935 he had purchased a living room suite. At my suggestion, this suite was removed from the house and the living room thoroughly cleaned. The patient immediately became symptom free.

Investigation of the suite of furniture showed that it was stuffed with sisal and Spanish moss. The patient reacted slightly to sisal by intradermal test. However, other exposures to sisal did not cause rhinitis.

Spanish moss from the furniture was extracted in Coca's solution. Scratch and intradermal tests with this extract showed very large reactions. To eliminate the possibility that this moss had been contaminated by some extraneous factor, such as molds, dust, or by chemical treatment, new unused Spanish moss was obtained from an upholsterer and an extract was made from this moss, using 1 Gm. of moss to 100 c.c. of Coca's solution. The total nitrogen of this extract was 1.0 mg. per cubic centimeter.

Using this new moss extract, 4 plus scratch reactions were obtained on testing the patient. Intradermal tests were positive with the original extract diluted 1:10,000,000. Passive transfer tests were done with the same extract and were also positive.

A small amount of the new moss was frozen with dry ice, ground to a powder, and insufflated into the patient's left nostril. Within three minutes, there occurred marked swelling of the membrane with a copious watery discharge, itching of the nose and eyes, and lacrimation, persisting three hours. This was an exact reproduction of the symptoms he had suffered when exposed to the upholstered furniture.

Due to the large amount of dilution to which the patient reacted on intradermal testing twenty-three individuals who had no history of "furniture sensitivity" were tested with the same extract. Fifteen of these were allergic to other substances and eight were, insofar as could be determined, nonallergic. All twenty-three subjects were tested by both the scratch and intradermal methods. In none were scratch tests positive. All individuals showed an increase in the size of the wheal on intradermal testing with the full-strength extract. Thirteen were negative with a 1:10 dilution, six with a 1:100 dilution, and three with a 1:1,000 dilution. One among the allergic individuals showed a positive test in a 1:1,000,000 dilution but a negative scratch test.

The patient described showed a positive intradermal test with a dilution of 1:10,000,000, and, as mentioned, showed a positive scratch test.

CONCLUSIONS

1. Spanish moss possesses antigenic properties, as proved in the case described, by (1) production of symptoms by deliberate contact, (2)

cessation of symptoms by removal of moss from the patient's environment, (3) production of skin reactions by extracts of moss fiber, and (4) the presence of transferable reagins as shown by positive passive transfer tests.

2. The skin of a person not allergic to the moss does not react to scratch tests with an extract containing 1.00 mg. of nitrogen per cubic centimeter, but does seem to react, in some cases at least, to intradermal testing with extracts containing up to 0.01 mg. total nitrogen per cubic centimeter.

REFERENCE

1. Metzger, F. C.; Spanish Moss, J. Florida M. A. 24: 99, 1937.

Society Proceedings

RESOLUTION

WHEREAS, the Society for the Study of Asthma and Allied Conditions has learned with deep sorrow of the death of Dr. H. B. Wilmer and

WHEREAS, the Society has sustained the loss of one of its honored and devoted members, the vice president elect of the Society and a member of the executive committee who was highly interested in the activities of the Society until his sudden death and

WHEREAS, his enthusiasm and personal interest in allergy and allied subjects have made him well known to all whose interests are in this field and

WHEREAS, his radiating and likeable personality endeared him to all who knew him,

RESOLVED, that we, The Society for the Study of Asthma and Allied Conditions, formally and sincerely record our great loss and misfortune in his untimely passing, and

RESOLVED, that a copy of this resolution be spread upon the minutes of the Society, that a copy be forwarded to his wife and family, and a notice be printed in THE JOURNAL OF ALLERGY.

(Signed)

W. C. SPAIN
HARRY L. ROGERS
MERLE M. MILLER

March 18, 1943.

Selected Abstracts

Asthma and Hay Fever

Under the Direction of Samuel M. Feinberg, M.D., and
Theodore T. Bernstein, M.D., Chicago

Allergy to Injectable Liver Extracts; Clinical and Immunological Observations. Feinberg, S. M., Alt, H. L., and Young, R. H.: Ann. Int. Med. **18**: 311, 1943.

A series of eight patients is presented in whom allergic reactions were produced after repeated injections of liver extract. The manifestations were mainly those of asthma and urticaria. The frequency of this type of allergy is suggested by the fact that six of these patients were from a total group of forty-eight treated for pernicious anemia. Scratch tests with injectable liver extracts produced positive reactions in all eight patients. Cutaneous and intracutaneous tests with fractions of liver and organ extracts of several species of animals indicate that one is dealing here neither with a species specificity nor an organ specificity involving the protein common to that organ. The specificity appears to be limited to a special organ fraction containing nitrogen but not giving true protein tests. The course of the allergy in these patients varied. The liver allergy occurring in atopic individuals had a tendency to persist, even after three and one-half years of observation. The allergy induced in the nonatopic persons displayed a tendency to disappear spontaneously. This paper calls attention to several important considerations. The clinical significance and importance of an allergy induced in such a high percentage of individuals cannot be ignored. The demonstration of an antigen residing in a fraction of organ tissue, and the fact that this antigen produces marked skin reactions without any evidence of the presence of protein, are immunologic findings that deserve further elaboration.

Influence of the Menstrual Cycle on the Titer of Circulating Reagins. Hans-Pruss, O. C., and Raymond, Ruth: J. Clin. Endocrinol. **3**: 81, 1943.

Since it is a rather common observation that allergic manifestations are aggravated in the premenstrual and menstrual periods, the authors

thought that perhaps it may be explained by an increase in reagins. They had previously demonstrated that the skin of the allergic female had the greatest reactivity during the last day of the catamenia. In the present experiment they tested the strength of the reagins of four young women who were sensitive to ragweed by doing passive transfer tests on five young males with blood taken at six different periods of the menstrual cycle. A site sensitized with undiluted serum was tested with 0.1 c.c. of a 1:1,000 dilution of ragweed pollen and the resulting wheal measured. The authors assumed that the size of the wheal was an indication of the concentration of the reagin. By this method they concluded that the serum of allergic women contains the highest reagin titer on the last day of menstruation. They also concluded that the reagin titer of allergic women is in inverse proportion to the estrogenic level.

Epinephrine and Ephedrine Analogues and Their Clinical Assay. Vaughan, W. T., Perkins, R. M., and Derbes, V. J.: J. Lab. & Clin. Med. **28**: 255, 1942.

The authors describe a scheme for the clinical assay of epinephrine, ephedrine, and their analogues, and the results obtained by these studies. The program consists of serial determinations of pulse rate, blood pressure and vital capacity; effect on histamine wheals and the local effect on one side of the nose as determined with the Glatzel-Mulinos mirror. For the general effects, hypodermic injections of the drug were used while for the nasal effect topical applications were made. Epinephrine and ephedrine were used as controls for comparison of the analogue studied. The results of these assays were checked by clinical trial. They observed that the failure of a particular analogue to be effective for one symptom did not necessarily mean that it was not effective for other allergic manifestations.

The Treatment of Food Allergy. Black, J. H.: South. M. J. **35**: 771, 1942.

In a series of one hundred asthmatic patients who had proven food allergy, desensitization was accomplished in five months in 73 per cent by graduated doses of the food orally administered. Most of these patients were sensitive to wheat, milk or egg. A control group of fifty patients who also had food allergy and asthma was observed for a five-month period without any attempt at desensitization except the complete avoidance of the food. In only 12 per cent of that group was the clinical sensitivity lost.

Dermatology

UNDER THE DIRECTION OF MARION B. SULZBERGER, M.D., NEW YORK, AND JOSEPH GOODMAN, M.D., BOSTON

A Comparative Study of Antigens of Human Pus, Mouse Brain and Chick Embryo Origin for the Diagnosis of Lymphogranuloma Venereum. Mortara, F., and Greenblatt, R. B.: Ven. Dis. Inform. **24**: 14, 1943.

Comparative studies of Frei antigens prepared from human pus, from mouse brain, and from chick embryos indicated that the chick embryo antigen was satisfactory and reliable. The authors particularly point out the fact that neither false positive nor false negative reactions were obtained with the chick embryo antigen. In addition the reactions to the chick embryo control were uncommon and slight when they did occur. The results obtained with the chick embryo antigen coincided with those obtained with the pus antigen and with those obtained from mouse brain antigen.

Experimental Studies With the Dermatophytes. IV. The Influence of Age Upon the Allergic Response in Experimental Ringworm in the Guinea Pig. DeLaMater, E. D.: J. Invest. Dermat. **5**: 423, 1942.

Using a strain of *Trichophyton gypseum*, the author studies the skin reactions of three groups of guinea pigs (newborn, middle aged, and adult) during and following ringworm infection. A study of these animals indicated that there was a gradual development of the ability to react allergically. Reactivity was at a low level in the newborn and developed progressively to a high level in the adults. It is concluded that in ringworm infections of the guinea pig there was a maturation factor, which may explain the observation that young animals are most susceptible to inoculation and progressive disease than are older animals.

Studies in Abnormal Human Sensitivity to Light. III. Passive Transfer of Light Hypersensitivity in Prurigo Aestivalis. Epstein, S.: J. Invest. Dermat. **5**: 285, 1942.

Passive transfer was attempted with serum with six patients suffering from prurigo aestivalis. In two instances there was a positive reaction, in one instance a doubtful reaction, and in three instances no reaction. In each instance it was attempted to elicit the reaction by exposure of the area injected with the patient's serum to ultraviolet light. In one instance the positive reaction was characterized by an urticarial response which appeared from seven to fifteen hours after exposure to the light. In the other instance of successful passive transfer, the injected area was exposed to the sun for about two hours. On the ninth day a prurigo-like eruption appeared in the injected area. The papules which made up this eruption persisted for about four days.

Studies in Abnormal Human Sensitivity to Light. IV. Photoallergic Concept of Prurigo Aestivalis. Epstein, S.: J. Invest. Dermat. **5**: 289, 1942.

The author reviews the theoretical background of reactions to light. He points out that there are in the main two types of light reactions, the photoallergic reaction and the phototoxic reaction. The evidence, as he reviews it, suggests that an allergic mechanism underlies the diseases known as eczema solare and urticaria photogenica. It is likewise probable that a photoallergic reaction is responsible for the production of the lesions of prurigo aestivalis, although it is admitted that factors other than sensitivity to light of allergic nature may contribute the pathogenesis of this disease.

"Red Moss" Dermatitis. Contact With Sponges Affecting Oystermen. Corson, E. F., and Pratt, A. G.: Arch. Dermat. & Syph. **47**: 574, 1943.

The authors describe an eruption which occurs on oystermen in the Middle Atlantic coast area. This eruption appears on the sides of the fingers, in severe cases spreading to the entire hand. The eruption is characterized by redness, scaling, and vesiculation.

An examination of the so-called "Red Moss" sponge which was the cause of this eruption revealed silicious spicules which made up part of the sponge. A positive patch test was obtained with the sponge, and a less strongly positive patch test was obtained with the spicules alone. The authors believe that the irritant affect of the spicules when embedded in the skin is the cause of the eruption. They do not believe that this dermatosis is allergic in nature.

Immunology

UNDER THE DIRECTION OF M. WALZER, M.D., AND MURRAY ALBERT, M.D., BROOKLYN

Studies of Precipitin-Production and Anaphylactic Sensitization in Guinea Pigs. Cohen, H. R., and Mosko, M. M.: J. Immunol. **46**: 59, 1943.

Guinea pigs are generally considered to be poor producers of precipitin. The influence of the method of antigen administration upon precipitin formation was investigated. One group of guinea pigs was sensitized with four intra-abdominal injections of crystalline egg albumen, given at three-day intervals. Another group received two intracardial injections. A third group received multiple intramuscular injections of egg albumen adsorbed on aluminum hydroxide cream. All animals were bled on the twenty-first day after the first injection, and the sera were titrated for precipitins by the antigen-dilution method.

In all three groups, intracardial injections of egg albumen resulted in severe or fatal anaphylactic shock. The highest precipitin titers were obtained with the aluminum cream preparation. Animals sensitized intra-abdominally often showed high precipitin titers, but the results obtained with this technique were inconsistent. Animals sensitized intracardially produced only slight amounts of precipitins, despite the fact that they could be fatally shocked by intracardial injection. The precipitin titers at twenty-one days were much higher than at fourteen days.

A number of guinea pigs were sensitized with a mixture of several antigens adsorbed on aluminum cream. Precipitins to these antigens were obtained in high titer. Staphylococcal toxin, given intracutaneously, failed to increase the precipitin-producing capacity of guinea pigs in this experiment.

The Experimental Demonstration That Periarteritis Nodosa Is a Manifestation of Hypersensitivity. Rich, A. R., and Gregory, J. E.: Bull. Johns Hopkins Hosp. **72**: 65, 1943.

In a previous communication, Rich reported a series of cases in which lesions of periarteritis nodosa were observed in patients who died, and were autopsied, shortly after having had serum sickness or hypersensitive reactions to sulfonamides. In the present studies, attempts were made to demonstrate experimentally in rabbits that periarteritis nodosa is a manifestation of hypersensitivity. The animals, when injected intravenously with large amounts of horse serum, usually developed febrile reactions and cutaneous flushes on the fifth or sixth day, corresponding to the symptoms of serum sickness in man. Rabbits were given an initial intravenous dose of 10 c.c. of normal horse serum per kilogram of body weight. A second group received sulfadiazine in addition to the horse serum. Many of the animals developed serum sickness. On the twelfth day, the rabbits showed positive skin reactions to tests with horse serum. These consisted of edema, developing within one-half hour. On the following day, delayed reactions developed consisting of large, elevated, erythematous lesions, often with a central area of hemorrhage and necrosis. These resembled Arthus reactions. On the seventeenth day, the animals received an intravenous injection of 1 c.c. of horse serum. Some of these rabbits were sacrificed and autopsied. Others received an additional intravenous dose of horse serum, or were continued on daily doses of sulfadiazine. Several days later, all animals were autopsied. The tissues of the rabbits treated with horse serum revealed arterial lesions in various stages, typical of periarteritis nodosa. These lesions consisted of edema of the media, necrosis, fibrinoid alteration, and hyalinization of the media, with infiltration of mononuclear and polymorphonuclear cells, including many eosinophiles. The administration of sulfadiazine had not influenced the course of the lesions. It was concluded that periarteritis nodosa can be

produced experimentally in rabbits, that it is a manifestation of anaphylactic sensitivity, and that it may follow single, as well as repeated doses of foreign serum.

Relationship of the Eosinophil Response to Factors Involved in Anaphylaxis. Campbell, D. H.: J. Infect. Dis. **72**: 42, 1943.

The effects of histamine, acetylcholine, adrenalin, and blood from shocked animals upon the eosinophilic response of guinea pigs were studied. Guinea pigs receiving multiple intra-abdominal injections of histamine, daily for several days, failed to show an increase in the percentage of eosinophiles in the blood. The same results were obtained with acetylcholine and cysteine. Each of these substances, however, enhanced the eosinophilic response in sensitized animals when shocked with antigen, or in normal animals receiving an injection of Ascaris keratin. The injection of the citrated blood of shocked animals into normal guinea pigs gave negative results, indicating the absence of an eosinophilotactic substance in the blood of the shocked animals. The continued injection of antigen into a sensitized animal resulted in a loss of the eosinophile response. Substances, such as adrenalin, which inhibit anaphylactic shock, also inhibited the eosinophilic response. Guinea pigs sensitized with sheep serum coupled with arsenalic acid, failed to show an eosinophilia following injection of the simple hapten. These animals were subsequently shown to be refractory to a shocking dose of the antigen used for sensitization. It was also demonstrated in guinea pigs sensitive to several antigens, that the diminution in eosinophilic response which followed repeated injections of an antigen was due to desensitization, and not to exhaustion of the eosinophile reserves. It was concluded that eosinophilia is more closely associated with the shock syndrome than with the primary antigen-antibody reaction. The function of eosinophiles during shock, and in normal animals, has not yet been determined, although the author believes that the function of eosinophiles is the same under all conditions.

Pediatrics

UNDER THE DIRECTION OF WILLIAM C. DEAMER, M.D., SAN FRANCISCO

An Association of Gastrointestinal Allergy With the Celiac Syndrome. McKhann, C. F., and Meserve, E. R.: J. Pediat. **22**: 362, 1943.

After reviewing various theories on the etiology of celiac disease, none of which are entirely acceptable, the authors call attention to the association of gastrointestinal allergy with the celiac syndrome. This association, in their experience, is frequent. Four cases of celiac disease are summarized, in all of which the evidence for gastrointestinal allergy

consisted chiefly in the presence of positive scratch or intradermal food tests. Following the elimination of the positive reactors, and other measures, however, improvement occurred in each case. Having been struck by the relationship between allergy and celiac disease, the authors then reviewed the records of patients with outspoken gastrointestinal allergy, and discovered two additional instances strongly suggesting the celiac syndrome.

Pursuing the study of gastrointestinal absorption in the allergic individual further, the authors demonstrated a decreased absorption of vitamin A, following a standard dose of this vitamin in oil, in three cases chosen for study. One of these suffered with atopic eczema, and two were asthmatic. Which may be primary, and which secondary, in the possible etiological association of allergy and celiac disease is not clear.

Allergic Dermatoses Due to Food Hypersensitivity. Report of a Delayed Skin Reaction Following Intracutaneous Inoculation of Autoserum. Wingard, R. M.: Arch Pediat. **60**: 139, 1943.

The author had, as his object, the demonstration of food atopen in the blood of patients with allergic dermatosis due to food. Two adults, and seven infants or children, with urticaria, angioneurotic edema, or atopic eczema, were given a food to which they were clinically sensitive. Five c.c. of blood were withdrawn at various intervals thereafter over a period of twenty-four hours. The specimens from an individual patient were pooled, and the serum then withdrawn. When this serum was reinjected intradermally a delayed skin reaction was obtained in six of the nine patients. In two of these, the reaction was an erythema 30 or 40 mm. in diameter; in the other four, it was a papule from 4 to 7 mm. in diameter. The author thought there was a resemblance in each instance between the experimental lesion and the clinical one. Control serums were not used.

Histaminase in the Treatment of Allergy in Children. Peshkin, M. M., Rapaport, H. G., Messer, W., Feuer, I., Siculer, A., and Berger, A.: J. Pediat. **22**: 427, 1943.

Forty-eight allergic children between 3 and 16 years of age, suffering with various allergic disorders, were given 50 units of histaminase daily for two to twenty weeks. The allergic complaints included asthma, hay fever, vasomotor rhinitis, urticaria, eszema, migraine, and physical allergy. The average duration of treatment was nine weeks. All forty-eight children failed to be relieved from the allergic syndrome for which the histaminase therapy was given. Two patients not in the series had discontinued taking histaminase because of nausea, vomiting and abdominal colic.

Match Test. Vollmer, H., Hyslop, H. W., and Lomant, H. V.: J. Pediat. **21**: 747, 1942.

A description is given of a new modification of skin testing which resembles the von Pirquet chisel abrasion method. It consists in a wooden stick the size of a match, the head of which is rendered abrasive with pumice particles cemented on with Duco cement. This head is impregnated with glycerinated extracts of various allergens. After 5 months of storage, positive tests were still elicited by pressing the head gently on the skin while twisting the match. Forty-seven individuals known to give positive tests to ragweed, June grass, orris root, egg white, or house dust, also gave positive match tests to the same substances. It is thought that since the method is almost entirely without pain, and less frightening and more casual, it represents an improvement over previous testing methods.

While the same technique can be employed for tuberculin testing, Schick testing, and vaccinating against smallpox, the results in these three instances are less satisfactory than the usual methods employed at present.

Coconut Water. Pradera, E. S., Fernandez, E., and Calderin, E. F.: Am. J. Dis. Child. **64**: 977, 1942.

The nutritive values of coconut water, and some potential uses for it, are discussed. It contains derived proteins of small molecular structure, which incorporate twelve amino acids covering almost all those considered necessary for optimum nutrition. Three attempts to sensitize rabbits with coconut water failed.

In addition, small amounts of sugar and neutral fats are present, as well as potassium, calcium, sodium, magnesium, chlorides and phosphates in an acid solution.

The report describes the use of coconut water in infants and children for both hypodermoclysis and venoclysis, the latter at the rate of 30 or 40 drops a minute for several hours. It also details successful feeding of twenty-three normal infants and several sick infants with mixtures of evaporated milk and coconut water.

Rhinology and Ophthalmology

UNDER THE DIRECTION OF FRENCH K. HANSEL, M.D., ST. LOUIS

The Relation of Ciliary Insufficiency to Death From Asthma and Other Respiratory Diseases. Hilding, A. C.: Ann. Otol., Rhin. & Laryng. **52**: 5, 1943.

A most outstanding contribution has been made by Hilding on the relation of ciliary insufficiency to death from asthma and other respiratory diseases. He points out that there is a group of cases among

patients who die from asthma who show a very striking and characteristic change in the bronchial epithelium. The change consists of a substitution of gobletlike cells for the normal columnar ciliated cells. Apparently it is a true metamorphosis. As this change takes place the ciliary mechanism is lost, and the characteristic viscid, mucinous secretion accumulates in the air passages. Normally this viscid secretion is very readily carried up vertical surfaces by ciliary action. The amount of secretion is enhanced because the erstwhile ciliary cells are secreting as well as the glands. The difficulty of removal of the secretion is aggravated because the mucin remains attached over large areas within the cells which produce it, thus anchoring the mass to the wall. When the air passages have become completely filled, the patient dies of asphyxia. In Hilding's opinion, this metamorphosis is the chief pathologic change, and death results directly from the loss of ciliary function.

He noted a second group of asthmatics in which the cilia were also lost, but the picture was essentially different. This group was characterized by chronic bronchitis with purulent secretion. There was destruction in the surface of the bronchial epithelium, and the ciliated cells had sloughed off very extensively. In these patients, also, the air passages filled up with secretion to such an extent that the patients died. Attention is also called to the fact that bronchospasm was doubtless a factor in some of these cases. In one of the group which was omitted from this discussion, spasm seemed to play a dominant role. In a patient with tracheobronchitis who died in extreme respiratory distress, the ciliated epithelium was practically entirely destroyed, and all the bronchi contained viscid plugs of secretion. Further studies were conducted on pathologic material from the pandemic of influenza in 1918. The material was not entirely satisfactory, but, as far as could be determined, the bronchiolar epithelium had been entirely destroyed and all the cilia with it.

In all of these groups, Hilding feels that the mechanical removal of the secretion as a substitute for ciliary action is indicated. Aspiration, either through a bronchoscope or a tracheotomy, would be the best.

Further studies are being conducted on the loss of ciliary function in the pneumonias. Nothing further can be reported at this time.

Head Infections in the Practice of Medicine. Shambaugh, G. E., Jr.: J. Iowa M. Soc. **31**: 373, 1941.

Shambaugh reports his observations on the differentiation of infectious and allergic rhinitis. In 102 consecutive cases of chronic nasal or sinal disease which he reviewed, the condition was essentially nasal with secondary involvement of the sinuses, in 51 cases. In 43 of these there was response to allergic treatment. In the other 51 cases the disturbance was primarily sinal, and in 36 of these a response to treat-

ment for allergy was obtained. He emphasizes that both the infection and the allergic condition must be treated in order to give maximum relief.

Vertigo Due to Obstruction of the Eustachian Tubes. Merica, F. W.: J. A. M. A. **118**: 1282, 1942.

Merica discusses his findings in 135 cases of vertigo due to tubal obstruction. Many of the patients had associated acute or chronic disease of the sinuses or ears. In fifteen instances the condition was associated with colds. Some patients obtained immediate relief from severe vertigo after inflation of the eustachian tubes. Some patients derived permanent relief from one inflation. Others had recurrence of symptoms and required repeated treatments. Some patients with eustachian tube obstruction proved to be allergic, and improved when the offending allergen was recognized and eliminated. Patients with a low metabolic rate had improved tubal patency after the administration of thyroid.

Allergy of the Eye. Bab, W.: Am. J. Ophth. **24**: 759, 1941.

Bab reports his observations on allergy of the eye in a group of 83 cases, in 41 of which there was edema of the eyelids. The etiologic agents varied greatly, and included sleeping pills (phanadorm) in one case, stewed cherries in another, strawberries in two others, and mechanical irritation such as that produced by plucking the eyebrows, squeezing the margin of the lid to straighten the lashes, and dyeing the eyebrows.

To Our Readers

The exigencies of the war situation have made it necessary to comply with the order of the War Production Board to reduce the weight of paper previously used for the JOURNAL. While this change will not affect the printed page it will affect the quality of the halftone illustrations. We regret that we have no choice in the matter and would ask the forbearance of our readers. As soon as the restrictions are removed, we shall resume our practice of printing the JOURNAL on the previously employed heavier grade of paper.

THE C. V. MOSBY CO., PUBLISHERS.

Correspondence

The Editor,
The Journal of Allergy.

My discussion of Dr. Myron Weitz' paper "Hypersensitivity to Insulin With Desensitization," published in the March issue of the JOURNAL, was omitted when this paper was published. I herewith resubmit it, and request that it be recorded.

A. H. FINEMAN.

New York City
Aug. 6, 1942

DR. ABRAHAM H. FINEMAN, NEW YORK.—Dr. Sigmund L. Friedman and I are reporting on five patients with insulin allergy whom we have observed and studied in the past two years at Sydenham Hospital.

These cases were skin tested with regular, protamine-zinc and crystalline insulin; and in all, passive transfer studies were done. Three showed markedly positive immediate skin reactions to all the insulins and one showed delayed reactions. In only one patient were reagins demonstrated in the blood with dilutions of serum up to 1:256. In three instances there was a history of an insulin-free period, and allergic symptoms developed only after the resumption of insulin therapy. In the other two cases, insulin allergy developed within ten days after insulin was first used.

Rapid desensitization was carried out in two cases over a period of five days, and tolerance to 16 units and 30 units per day, respectively, was reached.

Our patients were testetd with beef, pork, and deinsulinized pancreatic tissue to rule out the possibility of species-specific and gland-specific sensitization. All were proven sensitive to insulin, per se.

It is important when recommending insulin in the treatment of diabetes and other conditions to consider the possible development of insulin allergy and to watch carefully for local as well as systemic manifestations.

Our patients showed many different and interesting features in the development of this allergy. They are characteristic of an artificially induced type of hypersensitiveness similar to that seen in serum disease and allergy from other injectable foreign proteins.

I might say that four of these patients were diabetic and one non-diabetic. One of the diabetics was a physician who had ragweed hay fever and showed reagins in the blood to ragweed pollen but not to insulin. We all know that reagins may be present in the blood in insulin allergy and disappear within six months to one year or more. As a rule, positive skin reactions disappear at a later date. We have observed that in one patient who was highly sensitive to insulin and went into collapse following a small injection. She subsequently lost her hypersensitiveness and showed no positive skin reactions two years later.